> d his

(FILE 'HOME' ENTERED AT 15:40:46 ON 11 DEC 2003)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, SCISEARCH, AGRICOLA' ENTERED AT
15:41:07 ON 11 DEC 2003
L1 107 S TZT-1027
L2 8 S SOBLIDOTIN
L3 110 S L1 OR L2
L4 1299 S ERK-MAP KINASE
L5 56850 S (MAP KINASE) OR (MAP KINASE KINASE) OR (MAP KINASE KINASE KIN
L6 56850 S L4 OR L5
L7 21737 S L6 (P) INHIBIT?
L8 12249 S PD98059 OR U1026 OR PD1843522
L9 30675 S L7 OR L8
L10 1 S L3 (P) L9
L11 97435 S VINCRISTINE
L12 35 S L11 (P) L3
L13 11 DUPLICATE REMOVE L12 (24 DUPLICATES REMOVED)

=> log y

	Type	L #	Hits	Search Text	DBs	Time Stamp	Comments	Error Definition	Errors
1	BRS	L1	7	tzt-1027	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/12/11 15:23			0
2	BRS	L2	3	(ERK-Map adj kinase) same inhibit$3	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/12/11 15:24			0
3	BRS	L3	1324	((Map adj kinase) or (Map adj kinase adj kinase) or (map adj kinase adj kinase adj kinase)) same inhibit$3	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/12/11 15:24			0
4	BRS	L4	145	pd98059 or u1026 or pd1843522	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/12/11 15:26			0
5	BRS	L5	0	1 same (2 or 3 or 4)	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/12/11 15:25			0
6	BRS	L6	45494	antitumor or anticancer	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/12/11 15:26			0
7	BRS	L7	3	4 same 6	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/12/11 15:33			0
8	BRS	L8	6760	vincristine	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/12/11 15:30			0

	Type	L #	Hits	Search Text	DBs	Time Stamp	Comments	Error Definition	Errors
9	BRS	L9	2	1 same 8	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/12/11 15:32			0
10	BRS	L10	1	soblidotin	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/12/11 15:32			0
11	BRS	L11	25	(2 or 3) same 6	USPAT; US-PGPUB; EPO; JPO; DERWENT	2003/12/11 15:34			0

```
=> fil reg
FILE 'REGISTRY' ENTERED AT 08:52:56 ON 11 DEC 2003
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   10 DEC 2003  HIGHEST RN 625425-12-9
DICTIONARY FILE UPDATES:  10 DEC 2003  HIGHEST RN 625425-12-9

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2003

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=> d ide can l1

L1   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2003 ACS on STN
RN   149606-27-9  REGISTRY
CN   L-Valinamide, N,N-dimethyl-L-valyl-N-[(1S,2R)-2-methoxy-4-[(2S)-2-[(1R,2R)-
     1-methoxy-2-methyl-3-oxo-3-[(2-phenylethyl)amino]propyl]-1-pyrrolidinyl]-1-
     [(1S)-1-methylpropyl]-4-oxobutyl]-N-methyl- (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   L-Valinamide, N,N-dimethyl-L-valyl-N-[2-methoxy-4-[2-[1-methoxy-2-methyl-3-
     oxo-3-[(2-phenylethyl)amino]propyl]-1-pyrrolidinyl]-1-(1-methylpropyl)-4-
     oxobutyl]-N-methyl-, [2S-[1[1R*(R*),2S*],2R*(1S*,2S*)]]-
OTHER NAMES:
CN   Auristatin PE
CN   Soblidotin
CN   TZT 1027
FS   PROTEIN SEQUENCE; STEREOSEARCH
MF   C39 H67 N5 O6
CI   COM
SR   CA
LC   STN Files:   ADISINSIGHT, ANABSTR, BIOSIS, BIOTECHNO, CA, CANCERLIT,
       CAPLUS, CEN, CIN, DRUGNL, DRUGUPDATES, EMBASE, IMSDRUGNEWS, IMSRESEARCH,
       IPA, MEDLINE, PHAR, PROMT, SYNTHLINE, TOXCENTER, USAN, USPATFULL

**RELATED SEQUENCES AVAILABLE WITH SEQLINK**

Absolute stereochemistry.  Rotation (-).
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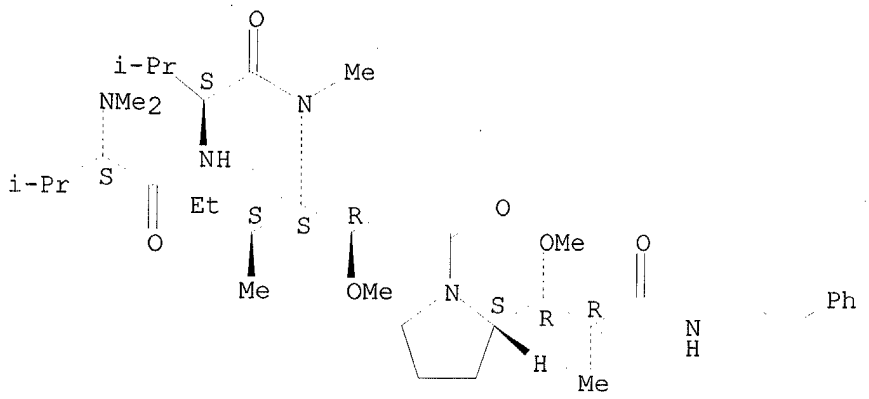

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

37 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
37 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 139:316667

REFERENCE 2: 139:255332

REFERENCE 3: 139:214714

REFERENCE 4: 139:7174

REFERENCE 5: 138:260510

REFERENCE 6: 137:272837

REFERENCE 7: 136:379569

REFERENCE 8: 136:303664

REFERENCE 9: 136:144822

REFERENCE 10: 136:48118

=> d ide can l16

L16 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS on STN
RN **142243-02-5** REGISTRY
CN Kinase (phosphorylating), mitogen-activated protein (9CI) (CA INDEX NAME)
OTHER NAMES:
CN ERK
CN ERK kinase
CN Erk receptor tyrosine kinase
CN ERK/MAP kinase
CN Extracellular signal-regulated kinase
CN Extracellular signal-regulated protein kinase
CN Gene ERK protein kinase
CN MAP kinase
CN MAP/ERK kinase
CN Mitogen-activated protein kinase
CN p43 MAP kinase
CN p43 Mitogen-activated protein kinase

CN p45 MAP kinase
DR 133876-94-5, 141349-99-7, 141350-00-7, 141616-09-3
MF Unspecified
CI MAN
SR CA
LC STN Files: ADISNEWS, AGRICOLA, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CEN, CIN, EMBASE, PROMT, TOXCENTER, USPAT2, USPATFULL

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
7944 REFERENCES IN FILE CA (1907 TO DATE)
32 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
7980 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 139:363402

REFERENCE 2: 139:363368

REFERENCE 3: 139:363317

REFERENCE 4: 139:362777

REFERENCE 5: 139:362735

REFERENCE 6: 139:362579

REFERENCE 7: 139:362161

REFERENCE 8: 139:362049

REFERENCE 9: 139:361886

REFERENCE 10: 139:361839

=> d his

(FILE 'HOME' ENTERED AT 08:16:11 ON 11 DEC 2003)
SET COST OFF

FILE 'REGISTRY' ENTERED AT 08:16:25 ON 11 DEC 2003
E TZT/CN
L1 1 S E6
E C39H67N5O6/MF
L2 7 S E3
L3 3 S L2 AND NC4/ES AND 46.150.18/RID
L4 2 S L3 NOT L1
SEL RN L1
L5 7 S E1/CRN

FILE 'HCAOLD' ENTERED AT 08:20:14 ON 11 DEC 2003
L6 0 S L1

FILE 'HCAPLUS' ENTERED AT 08:20:14 ON 11 DEC 2003
L7 37 S L1
L8 31 S TZT1027 OR TZT 1027 OR SOBLIDOTIN? OR AURISTATIN? PE

FILE 'HCAOLD' ENTERED AT 08:20:21 ON 11 DEC 2003
L9 0 S L1

FILE 'HCAPLUS' ENTERED AT 08:20:22 ON 11 DEC 2003
L10 37 S L1
L11 46 S TZT1027 OR TZT 1027 OR SOBLIDOTIN? OR AURISTATIN? PE OR AURIS

```
L12          53 S L10,L11
L13           9 S L12 AND (KOHNO ? OR WATANABE ?)/AU
L14          21 S L12 AND TEIKOKU?/PA,CS
L15           1 S L12 AND (WO2000-JP2 OR JP99-2971)/AP,PRN

     FILE 'REGISTRY' ENTERED AT 08:47:20 ON 11 DEC 2003
L16           1 S 142243-02-5

     FILE 'HCAPLUS' ENTERED AT 08:48:03 ON 11 DEC 2003
L17        7980 S L16
L18         367 S ERK(A)MAP()KINASE
L19       12817 S MITOGEN ACTIVATED PROTEIN KINASE
L20         699 S EXTRACELLULAR SIGNAL REGULATED PROTEIN KINASE
L21       12557 S MAP KINASE
L22        4309 S EXTRACELLULAR SIGNAL REGULATED KINASE
L23        2526 S ERK KINASE
L24           1 S L12 AND L17-L23
                E ANTITUMOR/CT
                E E5+ALL
L25      165939 S E1,E2
L26       20279 S E25,E26
                E E25+ALL
L27        1545 S E3
L28          40 S L12 AND L25-L27
L29          53 S L12,L13-L15,L24,L28
L30          20 S L29 AND (PD<=19990108 OR PRD<=19990108 OR AD<=19990108)

     FILE 'REGISTRY' ENTERED AT 08:52:56 ON 11 DEC 2003

=> fil hcaplus
FILE 'HCAPLUS' ENTERED AT 08:53:14 ON 11 DEC 2003
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FILE COVERS 1907 - 11 Dec 2003  VOL 139 ISS 24
FILE LAST UPDATED: 10 Dec 2003  (20031210/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

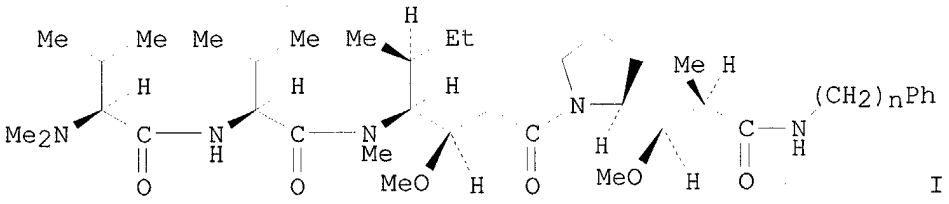
=> d l30 all hitstr tot

L30  ANSWER 1 OF 20  HCAPLUS  COPYRIGHT 2003 ACS on STN
AN   2003:714780  HCAPLUS
DN   139:214714
ED   Entered STN:  12 Sep 2003
TI   Synthesis and antineoplastic activity of dolastatin 10-related
     tetrapeptide phenethylamides
IN   Pettit, George R.; Barkoczy, Jozsef
PA   Arizona Board of Regents, USA
```

SO Mex. Pat. Appl., 37 pp.
CODEN: MXXXA3
DT Patent
LA Spanish
IC ICM C07D207-06
ICS A61K031-40
CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI MX 9307573	A	20000531	MX 1993-7573	19931201 <--
PRAI MX 1993-7573		19931201 <--		

GI



I

AB Dolastatin 10 is a lineal peptide that has strong antineoplastic activity against various cancers. Dolastatin 10-related tetrapeptide phenethylamides I (n = 1, 2, or 3) were synthesized and their antineoplastic activities determined The members of this group have demonstrated important antineoplastic activity against the cellular lines of human cancer. Tetrapeptides I are particularly active against human cell lines OVCAR-3 (ovary), SF-295 (central nervous system), A498 (renal), NCI-460 (lung), KM20L2 (colon), and SK-MEL-3 (melanoma).

ST dolastatin 10 analog tetrapeptide phenethylamide prepn antineoplastic

IT **Antitumor agents**
Human
Neoplasm
(synthesis and antineoplastic activity of dolastatin 10-related tetrapeptide phenethylamides)

IT Peptides, preparation
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesis and antineoplastic activity of dolastatin 10-related tetrapeptide phenethylamides)

IT 110417-88-4DP, Dolastatin 10, fragments **149606-27-9P**
149606-29-1P 149632-85-9P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesis and antineoplastic activity of dolastatin 10-related tetrapeptide phenethylamides)

IT 64-04-0, Benzeneethanamine 100-46-9, Benzenemethanamine, reactions
2038-57-5, Benzenepropanamine 120205-50-7 133120-90-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis and antineoplastic activity of dolastatin 10-related tetrapeptide phenethylamides)

IT 149606-89-3P 149606-91-7P 149606-92-8P 159525-38-9P 159525-40-3P
159525-42-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis and antineoplastic activity of dolastatin 10-related

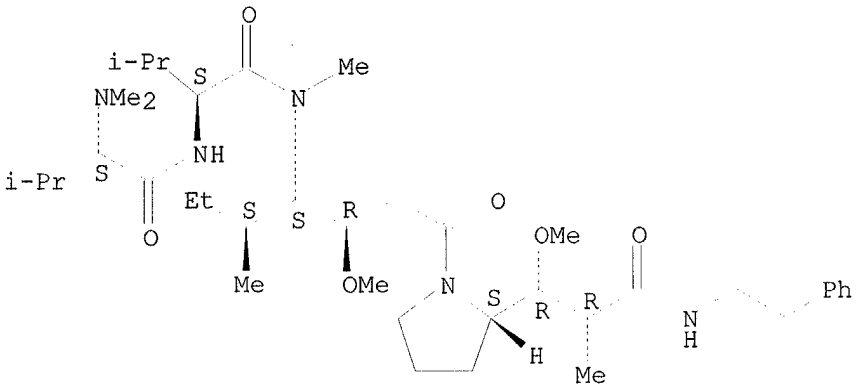
tetrapeptide phenethylamides)

IT **149606-27-9P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesis and antineoplastic activity of dolastatin 10-related tetrapeptide phenethylamides)

RN 149606-27-9 HCAPLUS

CN L-Valinamide, N,N-dimethyl-L-valyl-N-[(1S,2R)-2-methoxy-4-[(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-[(2-phenylethyl)amino]propyl]-1-pyrrolidinyl]-1-[(1S)-1-methylpropyl]-4-oxobutyl]-N-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L30 ANSWER 2 OF 20 HCAPLUS COPYRIGHT 2003 ACS on STN
AN 2000:475559 HCAPLUS
DN 133:94552
ED Entered STN: 14 Jul 2000
TI Antitumor agents
IN **Kohno, Michiaki; Watanabe, Kazushi**
PA **Teikoku Hormone Mfg. Co., Ltd., Japan**
SO PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
IC ICM A61K045-00
ICS A61K038-08; A61K035-00
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000040268	A1	20000713	WO 2000-JP2	20000104 <--
	W: AU, CA, JP, KR, US				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	CA 2358491	AA	20000713	CA 2000-2358491	20000104 <--
	EP 1142583	A1	20011010	EP 2000-900040	20000104 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
PRAI	JP 1999-2971	A	19990108 <--		
	WO 2000-JP2	W	20000104 <--		

AB When an antitumor agent acting on microtubule is used together with an **ERK MAP kinase** cascade blocking agent, the antitumor effect of the agent acting on microtubule can be remarkably potentiated. Namely, a combination of the agent acting on microtubule

with the **ERK MAP kinase** cascade blocking agent is useful as an excellent antitumor agent with a remarkable efficacy. Injection solns. were formulated containing **TZT-1027** 0.2 mg and isotonic NaCl solution q.s./ampule and were used in combination with tablets containing an **ERK MAP kinase** cascade blocking agent.

ST antitumor injection soln **TZT1027** PD98059

IT **Antitumor agents**
(antitumor agents containing microtubule polymerization inhibitors and **ERK MAP kinase** cascade blocking agent)

IT Microtubule
(polymerization inhibitors; antitumor agents containing microtubule polymerization inhibitors and **ERK MAP kinase** cascade blocking agent)

IT Drug delivery systems
(tablets; antitumor agents containing microtubule polymerization inhibitors and **ERK MAP kinase** cascade blocking agent)

IT **142243-02-5, MAP kinase**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ERK, cascade blockers; antitumor agents containing microtubule polymerization inhibitors and **ERK MAP kinase** cascade blocking agent)

IT 167869-21-8, PD98059
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antitumor agents containing microtubule polymerization inhibitors and **ERK MAP kinase** cascade blocking agent)

IT **149606-27-9, TZT-1027**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antitumor agents containing microtubule polymerization inhibitors and **ERK MAP kinase** cascade blocking agent)

RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Anon; HCAPLUS
(2) Anon; HCAPLUS
(3) Kazuto, N; Cancer and Chemotherapy (Gan to kagaku ryoho) 1997, V24(15), P2213
(4) Kazuto, N; Int J Cancer 1995, V63(5), P688
(5) Kazuya, F; Science and Chemotherapy 1997, V24(11), P1519
(6) Townsend, K; Oncogene 1998, V17(10), P1223 HCAPLUS
(7) Yoichi, N; New Medicine (Saishin Igaku) 1997, V52(12), P2700

IT **142243-02-5, MAP kinase**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ERK, cascade blockers; antitumor agents containing microtubule polymerization inhibitors and **ERK MAP kinase** cascade blocking agent)

RN 142243-02-5 HCAPLUS

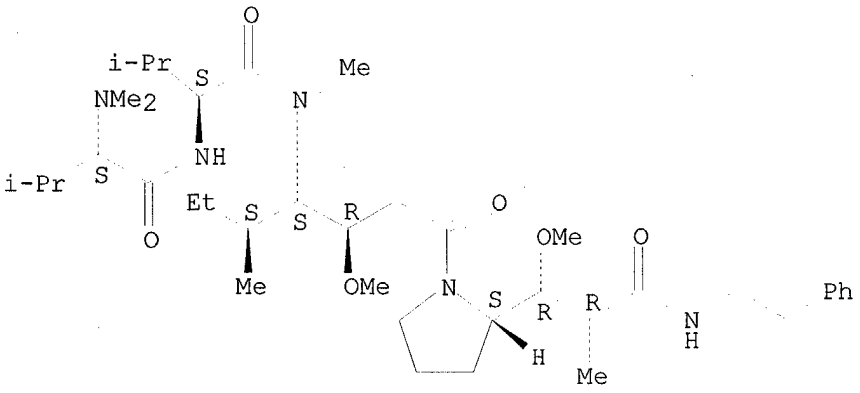
CN Kinase (phosphorylating), mitogen-activated protein (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT **149606-27-9, TZT-1027**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antitumor agents containing microtubule polymerization inhibitors and **ERK MAP kinase** cascade blocking agent)

RN 149606-27-9 HCAPLUS
CN L-Valinamide, N,N-dimethyl-L-valyl-N-[(1S,2R)-2-methoxy-4-[(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-[(2-phenylethyl)amino]propyl]-1-pyrrolidinyl]-1-[(1S)-1-methylpropyl]-4-oxobutyl]-N-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L30 ANSWER 3 OF 20 HCAPLUS COPYRIGHT 2003 ACS on STN
AN 2000:464927 HCAPLUS
DN 133:84247
ED Entered STN: 11 Jul 2000
TI Antitumor agents containing dolastatin 10 or its analogs and other antitumor agents
IN Mikami, Takashi; Kobayashi, Motohiro; Natsume, Akitaka; **Watanabe, Junichi**; Miyazaki, Koichi
PA **Teikoku Hormone Mfg. Co., Ltd., Japan**
SO Jpn. Kokai Tokkyo Koho, 6 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
IC ICM A61K038-00
ICS A61P035-00; A61K031-337; A61K031-505; A61K031-66; A61K031-704; A61K031-7048; A61K033-24
CC 1-6 (Pharmacology)
Section cross-reference(s): 63
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI JP 2000191546	A2	20000711	JP 1998-373475	19981228 <--
PRAI JP 1998-373475		19981228 <--		

AB Antitumor agents contain (A) dolastatin 10 or its analogs and (B) 5-fluorouracil (I), doxorubicin, irinotecan, cisplatin, cyclophosphamide, etoposide, and/or paclitaxel as active ingredients. Concomitant or sep. use of compound in A and compd(s). B is also claimed. I.v. injection of **TZT-1027** at 0.75 mg/kg and I at 37.5 mg/kg resulted in 95% survival rate in L1210-bearing mice.
ST antitumor **TZT1027** fluorouracil; dolastatin doxorubicin irinotecan cisplatin antitumor; cyclophosphamide etoposide paclitaxel dolastatin antitumor
IT 50-18-0D, Cyclophosphamide, mixts. containing 51-21-8D, 5-Fluorouracil, mixts. containing 15663-27-1D, Cisplatin, mixts. containing 23214-92-8D, Doxorubicin, mixts. containing 33069-62-4D, Paclitaxel, mixts. containing 33419-42-0D, Etoposide, mixts. containing 97682-44-5D, Irinotecan, mixts. containing 110417-88-4D, Dolastatin 10, mixts. containing **149606-27-9D**, **TZT-1027**, mixts. containing 280744-16-3 280744-17-4 280744-18-5 280744-19-6 280744-20-9 280744-21-0 280744-22-1

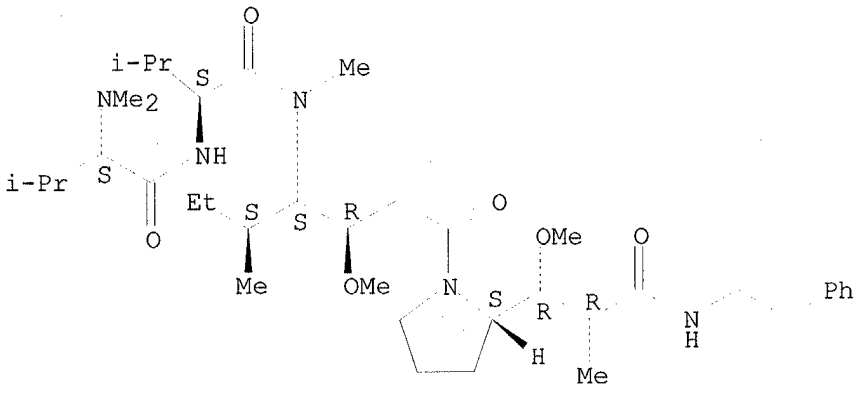
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antitumor agents containing dolastatin 10 or its analogs and other antitumor agents)

IT **149606-27-9D, TZT-1027,** mixts. containing
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antitumor agents containing dolastatin 10 or its analogs and other antitumor agents)

RN 149606-27-9 HCAPLUS

CN L-Valinamide, N,N-dimethyl-L-valyl-N-[(1S,2R)-2-methoxy-4-[(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-[(2-phenylethyl)amino]propyl]-1-pyrrolidinyl]-1-[(1S)-1-methylpropyl]-4-oxobutyl]-N-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L30 ANSWER 4 OF 20 HCAPLUS COPYRIGHT 2003 ACS on STN

AN 1999:760746 HCAPLUS

DN 132:117225

ED Entered STN: 02 Dec 1999

TI Modulation of cIAP-1 by novel antitubulin agents when combined with bryostatin 1 results in increased apoptosis in the human early pre-B acute lymphoblastic leukemia cell line reh

AU Wall, Nathan R.; Mohammad, Ramzi M.; Nabha, Sanaa M.; Pettit, George R.; Al-Katib, Ayad M.

CS Division of Hematology and Oncology, Department of Internal Medicine, Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, MI, 48201, USA

SO Biochemical and Biophysical Research Communications (**1999**), 266(1), 76-80
CODEN: BBRCA9; ISSN: 0006-291X

PB Academic Press

DT Journal

LA English

CC 1-6 (Pharmacology)

AB Previous studies have shown that bryostatin 1 induces a decrease in the expression of the antiapoptotic protooncogene Bcl-2 in the human acute lymphoblastic leukemia (ALL) cell line Reh. This down-regulation has been shown to reduce drug resistance of the Reh cells to anti-tubulin polymerization agents. In the present study we investigated the effect of bryostatin 1 alone and in combination with novel anti-tubulin agents (dolastatin 10 and **auristatin PE**) and the chemotherapeutic vincristine on the inhibitor of apoptosis protein cIAP-1. Cells were cultured with bryostatin 1 (1 nM), dolastatin 10 (0.1 ng/mL), **auristatin**

PE (0.1 ng/mL), or vincristine (0.5 ng/mL) alone or the combination of these anti-tubulins with bryostatin 1. Western blots were conducted to assess the effects of the above agents on cIAP-1 protein level. Flow-cytometric anal. [7-amino-actinomycin D (7AAD)] was conducted to assess apoptosis as well as staining for morphol. using tetrachrome stain. Our results show that cIAP-1 is induced in a time-dependent fashion after bryostatin 1 exposure up to 72 h. However, upon treatment of cells with a combination of bryostatin 1 and dolastatin 10 or **auristatin PE**, the induction of cIAP-1 was abolished, leading to a significant increase in apoptosis. The initial 24- and 48-h reduction in cIAP-1 protein level recorded in the bryostatin 1 and vincristine combination recovered to control levels by 72 h. We believe that this phenomenon is responsible for the reduced apoptosis recorded in this combination. Results of this study should prove useful in guiding the clin. application of these novel agents in the treatment of ALL. (c) 1999 Academic Press.

ST bryostatin dolastatin **auristatin** antileukemic cIAP1 Bcl2; acute lymphoblastic leukemia apoptosis bryostatin dolastatin; vincristine bryostatin interaction antileukemic resistance cIAP1

IT **Antitumor agents**

IT Leukemia
(acute pre-B-cell, inhibitors of; cIAP-1 modulation by novel antitubulin agents when combined with bryostatin 1 results in increased apoptosis in the human early pre-B ALL cell line reh)

IT Drug resistance
(antitumor; cIAP-1 modulation by novel antitubulin agents when combined with bryostatin 1 results in increased apoptosis in the human early pre-B ALL cell line reh)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(bcl-2; cIAP-1 modulation by novel antitubulin agents when combined with bryostatin 1 results in increased apoptosis in the human early pre-B ALL cell line reh)

IT Apoptosis
Drug interactions
(cIAP-1 modulation by novel antitubulin agents when combined with bryostatin 1 results in increased apoptosis in the human early pre-B ALL cell line reh)

IT Tubulins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(cIAP-1 modulation by novel antitubulin agents when combined with bryostatin 1 results in increased apoptosis in the human early pre-B ALL cell line reh)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(cIAP1; cIAP-1 modulation by novel antitubulin agents when combined with bryostatin 1 results in increased apoptosis in the human early pre-B ALL cell line reh)

IT 57-22-7, Vincristine 83314-01-6, Bryostatin 1 110417-88-4, Dolastatin 10 **149606-27-9, Auristatin PE**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(cIAP-1 modulation by novel antitubulin agents when combined with bryostatin 1 results in increased apoptosis in the human early pre-B ALL cell line reh)

RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD

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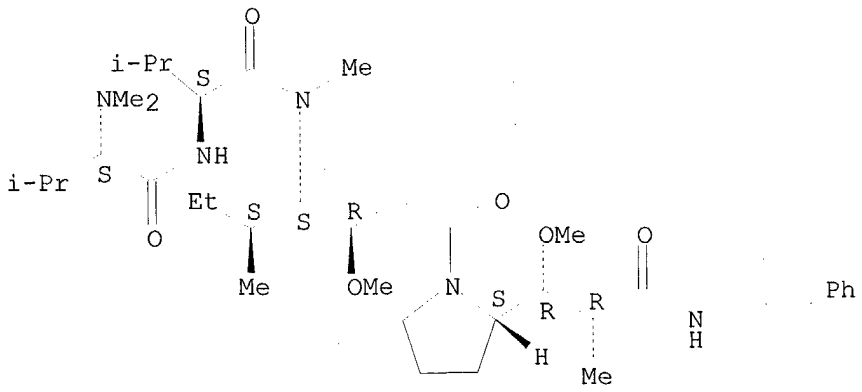
IT **149606-27-9, Auristatin PE**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(cIAP-1 modulation by novel antitubulin agents when combined with bryostatin 1 results in increased apoptosis in the human early pre-B ALL cell line reh)

RN 149606-27-9 HCAPLUS

CN L-Valinamide, N,N-dimethyl-L-valyl-N-[(1S,2R)-2-methoxy-4-[(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-[(2-phenylethyl)amino]propyl]-1-pyrrolidinyl]-1-[(1S)-1-methylpropyl]-4-oxobutyl]-N-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L30 ANSWER 5 OF 20 HCAPLUS COPYRIGHT 2003 ACS on STN
AN 1999:605621 HCAPLUS
DN 132:175392
ED Entered STN: 24 Sep 1999
TI Bax:Bcl-2 ratio modulation by bryostatin 1 and novel antitubulin agents is important for susceptibility to drug induced apoptosis in the human early pre-B acute lymphoblastic leukemia cell line, Reh
AU Wall, N. R.; Mohammad, R. M.; Al-Katib, A. M.
CS Department of Internal Medicine, Division of Hematology and Oncology, Karmanos Cancer Institute and Wayne State University School of Medicine, Detroit, MI, USA
SO Leukemia Research (**1999**), 23(10), 881-888
CODEN: LEREDD; ISSN: 0145-2126
PB Elsevier Science Ltd.
DT Journal
LA English
CC 1-6 (Pharmacology)
AB The ratio of Bax to Bcl-2 protein can determine whether cells will die via apoptosis or be protected from it. Reh was found to express a high basal level of Bcl-2 but was lacking of Bax protein expression. Treatment with bryostatin 1 induced a down-regulation in Bcl-2 protein that was not accompanied by an obvious Bax protein induction or apoptosis. These results suggest that a decreased level of Bcl-2 alone in this cell line is not sufficient for apoptosis induction. In an effort to identify the mechanism whereby apoptosis could be induced in this ALL model, we treated Reh cells with three microtubule inhibitors: dolastatin 10, **auristatin PE** and vincristine, in the presence and absence of bryostatin 1. When used alone, only dolastatin 10 induced apoptosis that was detected morphol., and by flow cytometry. Western blots revealed that dolastatin 10-induced apoptosis was accompanied by the induction of Bax protein and the reduction in Bcl-2 protein. **Auristatin PE** and vincristine induced both Bax and Bcl-2 protein, leaving the Bax:Bcl-2 ratio constant Reh cells pretreated for 24 h with bryostatin 1 followed by dolastatin 10, **auristatin PE** or vincristine showed significant apoptosis which was accompanied by Bcl-2 protein down regulation and Bax protein up regulation. We conclude that: (1) expression of bax is necessary for apoptosis-induction in this model; (2) a decrease in Bcl-2 level alone is not sufficient and might not be necessary for apoptosis-induction; and (3) the ratio of Bax:Bcl-2 plays a critical role in susceptibility to apoptosis in Reh cells. The results from this study should prove useful in guiding the clin. application of these novel agents in the treatment of acute lymphoblastic leukemia.
ST Bax Bcl2 protein apoptosis lymphoblastic leukemia bryostatin antitubulin
IT **Antitumor agents**
(B-cell leukemia; Bax:Bcl-2 ratio modulation by bryostatin 1 and antitubulin agents is important for susceptibility to apoptosis in human early pre-B acute lymphoblastic leukemia)
IT Leukemia
(B-cell prolymphocytic; Bax:Bcl-2 ratio modulation by bryostatin 1 and antitubulin agents is important for susceptibility to apoptosis in human early pre-B acute lymphoblastic leukemia)
IT Apoptosis
Drug interactions
(Bax:Bcl-2 ratio modulation by bryostatin 1 and antitubulin agents is important for susceptibility to apoptosis in human early pre-B acute lymphoblastic leukemia)
IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Bax; Bax:Bcl-2 ratio modulation by bryostatin 1 and antitubulin agents is important for susceptibility to apoptosis in human early pre-B acute

lymphoblastic leukemia)

IT **Antitumor agents**
(acute lymphocytic leukemia; Bax:Bcl-2 ratio modulation by bryostatin 1 and antitubulin agents is important for susceptibility to apoptosis in human early pre-B acute lymphoblastic leukemia)

IT Leukemia
(acute lymphocytic; Bax:Bcl-2 ratio modulation by bryostatin 1 and antitubulin agents is important for susceptibility to apoptosis in human early pre-B acute lymphoblastic leukemia)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(bcl-2; Bax:Bcl-2 ratio modulation by bryostatin 1 and antitubulin agents is important for susceptibility to apoptosis in human early pre-B acute lymphoblastic leukemia)

IT 57-22-7, Vincristine 83314-01-6, Bryostatin 1 110417-88-4, Dolastatin 10 **149606-27-9, Auristatin PE**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Bax:Bcl-2 ratio modulation by bryostatin 1 and antitubulin agents is important for susceptibility to apoptosis in human early pre-B acute lymphoblastic leukemia)

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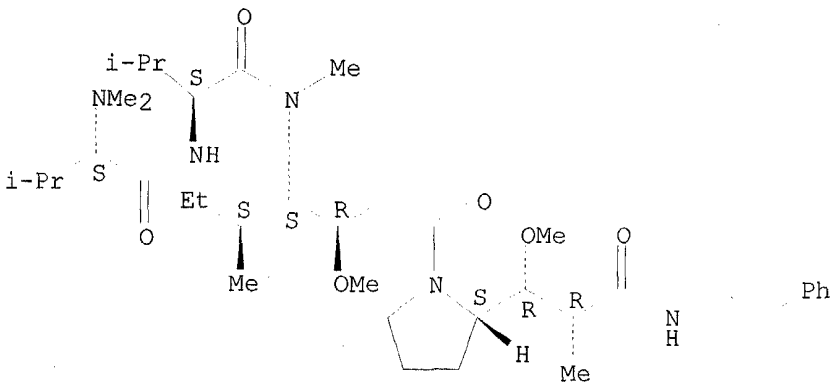
IT **149606-27-9, Auristatin PE**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(Bax:Bcl-2 ratio modulation by bryostatin 1 and antitubulin agents is important for susceptibility to apoptosis in human early pre-B acute lymphoblastic leukemia)

RN 149606-27-9 HCAPLUS

CN L-Valinamide, N,N-dimethyl-L-valyl-N-[(1S,2R)-2-methoxy-4-[(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-[(2-phenylethyl)amino]propyl]-1-pyrrolidinyl]-1-[(1S)-1-methylpropyl]-4-oxobutyl]-N-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L30 ANSWER 6 OF 20 HCAPLUS COPYRIGHT 2003 ACS on STN
AN 1999:501285 HCAPLUS
DN 132:58808
ED Entered STN: 12 Aug 1999
TI A new tubulin polymerization inhibitor, **auristatin PE**, induces tumor regression in a human Waldenstrom's macroglobulinemia xenograft model
AU Mohammad, Ramzi M.; Limvarapuss, Chainarong; Wall, Nathan R.; Hamdy, Nayera; Beck, Frances W. J.; Pettit, George R.; Al-Katib, Ayad
CS Division of Hematology and Oncology, Department of Internal Medicine, Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, MI, 48201, USA
SO International Journal of Oncology (**1999**), 15(2), 367-372
CODEN: IJONES; ISSN: 1019-6439
PB International Journal of Oncology
DT Journal
LA English
CC 1-6 (Pharmacology)

AB Waldenstrom's macroglobulinemia (WM) is an uncommon lymphoproliferative disease which remains incurable with current treatment protocols. We have previously established a permanent WM cell line, WSU-WM, which grows as a xenograft in severe combined immune deficient (SCID) mice. In this study, we investigated the anti-tumor effects of **auristatin PE** (a structural modification of the marine, shell-less mollusk peptide constituent dolastatin 10). WSU-WM cells were cultured in RPMI-1640 at a concentration of 2+105 cells/mL using 24-well plates. **Auristatin PE** or dolastatin 10 were added to triplicate wells and cell count and viability were assessed after 24, 48 and 72 h. Results showed that both agents were active against WSU-WM, and were able to induce complete growth inhibition at 100 pg/mL. The efficacy of these agents in vivo was evaluated using the WSU-WM SCID mouse xenograft model. **Auristatin PE** and dolastatin 10 were give i.v. via tail vein at 2.0 mg/kg and 0.2 mg/kg, resp. The agents were given every second day for three injections which represent the maximum tolerated doses. Tumor growth inhibition (T/C), tumor growth delay (T-C), and log10 kill for **auristatin PE** and dolastatin 10 were 0%, 18 days, 2.83 and 67%, 2 days, 0.06, resp. Based on these animal results, dolastatin 10 was inactive while **auristatin PE** was highly active. We therefore focused further investigation on **auristatin PE** to understand some of its mechanisms of action. Using two flow cytometry assays, propidium iodide for cell cycle anal. and 7-amino actinomycin D (7AAD) to detect apoptosis, we were able to demonstrate that **auristatin PE** at 10 pg/mL after 24 h arrested 50% of WSU-MW cells in G2M. Concomitantly, 31% of **auristatin PE**-treated cells entered apoptosis. By 72 h, greater than 75% of the cells became apoptotic. The activity of **auristatin PE** should be evaluated in other tumor types and in clin. trials.

ST tubulin polymn inhibitor **auristatin PE** tumor regression Waldenstrom macroglobulinemia

IT Lymphoproliferative disorders
(Waldenstrom's macroglobulinemia; new tubulin polymerization inhibitor, **auristatin PE**, induces tumor regression in a human Waldenstrom's macroglobulinemia xenograft model)

IT **Antitumor agents**
Apoptosis
Cell cycle
(new tubulin polymerization inhibitor, **auristatin PE**, induces tumor regression in a human Waldenstrom's macroglobulinemia xenograft model)

IT 110417-88-4, Dolastatin 10
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effect of **auristatin PE** and dolastatin in a human Waldenstrom's macroglobulinemia xenograft model)

IT **149606-27-9, Auristatin PE**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(new tubulin polymerization inhibitor, **auristatin PE**, induces tumor regression in a human Waldenstrom's macroglobulinemia xenograft model)

RE.CNT 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD

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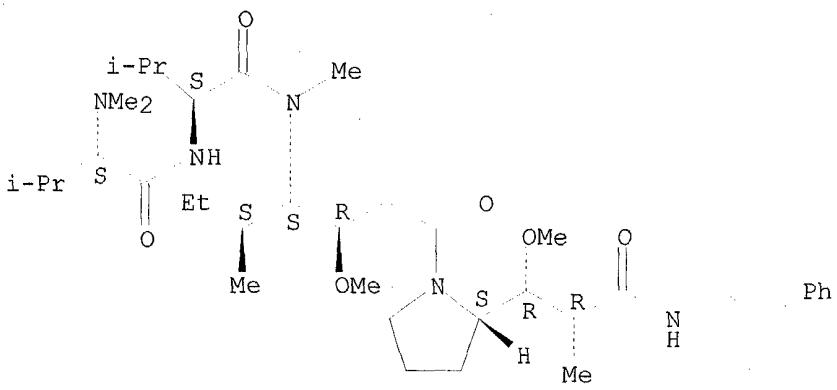
IT **149606-27-9, Auristatin PE**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(new tubulin polymerization inhibitor, **auristatin PE**, induces tumor regression in a human Waldenstrom's macroglobulinemia xenograft model)

RN 149606-27-9 HCAPLUS

CN L-Valinamide, N,N-dimethyl-L-valyl-N-[(1S,2R)-2-methoxy-4-[(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-[(2-phenylethyl)amino]propyl]-1-pyrrolidinyl]-1-[(1S)-1-methylpropyl]-4-oxobutyl]-N-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L30 ANSWER 7 OF 20 HCAPLUS COPYRIGHT 2003 ACS on STN
AN 1999:409245 HCAPLUS
DN 131:63482
ED Entered STN: 02 Jul 1999
TI anticancer **TZT-1027** microspheres
IN Noda, Junichiro; Kobayashi, Motohiro; Sakata, Junichi
PA **Teikoku Hormone Mfg. Co., Ltd., Japan**
SO Jpn. Kokai Tokkyo Koho, 5 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
IC ICM A61K038-00
ICS A61K009-16; A61K047-30; A61K035-56
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1
FAN.CNT 1
PATENT NO. KIND DATE APPLICATION NO. DATE

PI	JP 11171787	A2	19990629	JP 1997-362289	19971212 <--
PRAI	JP 1997-362289		19971212 <--		

AB Slow-release anticancer **TZT-1027** microspheres are prepared with copolymer of lactic acid and glycolic acid at 40 : 60- 60 : 40 and having mol. weight of 4000-6000. The microspheres are prepared by the O/W emulsion drying method.

ST anticancer **TZT1027** microsphere

IT **Antitumor agents**
Dissolution rate
(anticancer **TZT-1027** microspheres)

IT Drug delivery systems
(microspheres, slow-release; anticancer **TZT-1027** microspheres)

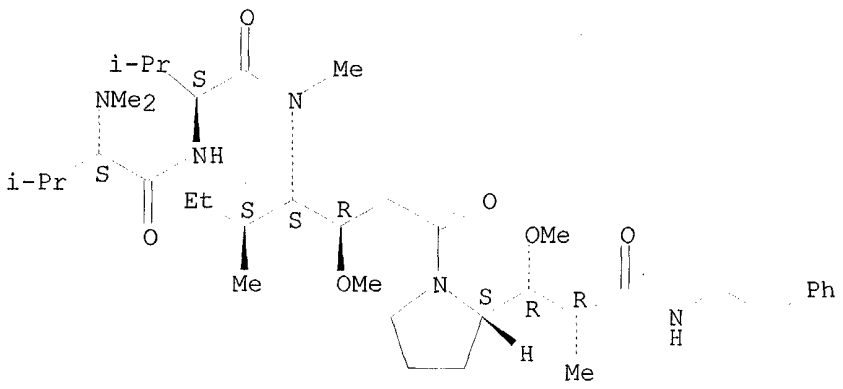
IT 34346-01-5, Lactic acid-glycolic acid copolymer **149606-27-9**, **Tzt-1027**
RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(anticancer **TZT-1027** microspheres)

IT **149606-27-9, Tzt-1027**
RL: PEP (Physical, engineering or chemical process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(anticancer **TZT-1027** microspheres)

RN 149606-27-9 HCAPLUS

CN L-Valinamide, N,N-dimethyl-L-valyl-N-[(1S,2R)-2-methoxy-4-[(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-[(2-phenylethyl)amino]propyl]-1-pyrrolidinyl]-1-[(1S)-1-methylpropyl]-4-oxobutyl]-N-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L30 ANSWER 8 OF 20 HCAPLUS COPYRIGHT 2003 ACS on STN

AN 1999:403133 HCAPLUS

DN 131:208482

ED Entered STN: 01 Jul 1999

TI **TZT-1027**: Antineoplastic

AU Hoshi, A.; Leeson, P.; Castaner, J.

CS Tokyo, 125-0061, Japan

SO Drugs of the Future (**1999**), 24(4), 404-409
CODEN: DRFUD4; ISSN: 0377-8282

PB Prous Science

DT Journal; General Review

LA English

CC 1-0 (Pharmacology)

AB A review, with 34 refs., on the preparation and pharmacol. activities of the antitumor drug **TZT-1027**.

ST review **TZT1027** antineoplastic leukemia colon carcinoma

IT **Antitumor agents**
(**TZT-1027**: antineoplastic)
IT **Antitumor agents**
(colon adenocarcinoma; **TZT-1027**: antineoplastic)
IT Intestine, neoplasm
Intestine, neoplasm
(colon, adenocarcinoma, inhibitors; **TZT-1027**: antineoplastic)
IT **Antitumor agents**
(leukemia; **TZT-1027**: antineoplastic)
IT **Antitumor agents**
(melanoma; **TZT-1027**: antineoplastic)
IT **Antitumor agents**
(solid tumor; **TZT-1027**: antineoplastic)
IT Drug interactions
(synergistic; ara-C combination with **TZT-1027**: antineoplastic activity)
IT **149606-27-9, TZT-1027**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**TZT-1027**: antineoplastic)
IT 147-94-4, Ara-c
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ara-C combination with **TZT-1027**: antineoplastic activity)
RE.CNT 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD
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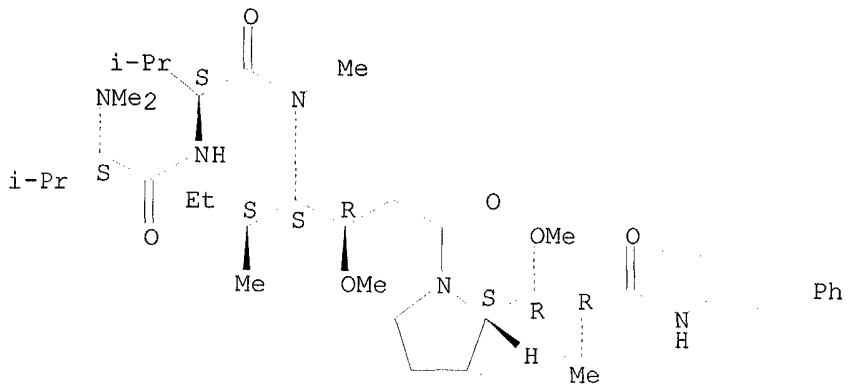
IT **149606-27-9, TZT-1027**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**TZT-1027**: antineoplastic)

RN 149606-27-9 HCAPLUS

CN L-Valinamide, N,N-dimethyl-L-valyl-N-[(1S,2R)-2-methoxy-4-[(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-[(2-phenylethyl)amino]propyl]-1-pyrrolidinyl]-1-[(1S)-1-methylpropyl]-4-oxobutyl]-N-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L30 ANSWER 9 OF 20 HCAPLUS COPYRIGHT 2003 ACS on STN
AN 1999:384468 HCAPLUS
DN 131:208737
ED Entered STN: 22 Jun 1999
TI Induction of growth inhibition and apoptosis in pancreatic cancer cells by **auristatin-PE** and gemcitabine
AU Li, YiWei; Singh, Brahmchetna; Ali, Nasima; Sarkar, Fazlul H.
CS Department of Pathology, Karmanos Cancer Institute at Wayne State University School of Medicine, Detroit, MI, USA
SO International Journal of Molecular Medicine (**1999**), 3(6), 647-653
CODEN: IJMMFG; ISSN: 1107-3756
PB International Journal of Molecular Medicine
DT Journal
LA English
CC 1-6 (Pharmacology)
AB Pancreatic adenocarcinoma is the fifth leading cause of cancer-related deaths in the United States. Treatment for this disease has largely been unsuccessful, which may partly be due to insufficient data regarding the mol. mechanisms of chemotherapeutic drugs currently being used as single agents or in combined modality regimens. In this study, the authors investigated the mol. mechanisms by which **auristatin-PE**, a newly developed exptl. agent, and gemcitabine, a com. available anti-cancer agent, exert their inhibitory effects on pancreatic cancer cell lines containing wild-type p53 (HPAC) and mutant p53 (PANC-1). The results showed that **auristatin-PE** and gemcitabine inhibited cell growth and induced cell cycle arrest in G2/M and S phase, resp. **Auristatin-PE** also induced apoptosis in both cell lines. Western blot anal. showed that **auristatin-**

PE up-regulated the expression of wt-p53, p21WAF1 and Bax, and down-regulated Bcl-2 and cyclin B in HPAC cells, while only up-regulation of p21WAF1 and Bax was observed in PANC-1 cells. These results suggest that **auristatin-PE** may induce apoptosis and p21WAF1 expression through p53-dependent or independent pathways, and that up-regulation of p21WAF1 and Bax and down-regulation of Bcl-2 may be the mol. mechanism through which **auristatin-PE** inhibits cell growth and induces apoptosis. Furthermore, the up-regulation of p21WAF1 and down-regulation of cyclin B may contribute to the G2/M cell cycle arrest. Combination of **auristatin-PE** and gemcitabine showed significantly greater inhibition of cell growth and up-regulated expression of p21WAF1 and Bax. From these results, the selection of therapeutic agents based on their mol. mechanism may improve therapeutic outcome, and **auristatin-PE** may be more effective in the treatment of pancreatic cancer when given in combination with gemcitabine, rather than as a single agent.

ST apoptosis pancreatic cancer cell **auristatin PE** gemcitabine

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Bax; induction of growth inhibition and apoptosis in pancreatic cancer cells by **auristatin-PE** and gemcitabine)

IT Proteins, specific or class
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(bcl-2; induction of growth inhibition and apoptosis in pancreatic cancer cells by **auristatin-PE** and gemcitabine)

IT Apoptosis
Cell proliferation
Pancreas, neoplasm
(induction of growth inhibition and apoptosis in pancreatic cancer cells by **auristatin-PE** and gemcitabine)

IT p53 (protein)
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(induction of growth inhibition and apoptosis in pancreatic cancer cells by **auristatin-PE** and gemcitabine)

IT Cyclin dependent kinase inhibitors
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(p21CIP1/WAF1; induction of growth inhibition and apoptosis in pancreatic cancer cells by **auristatin-PE** and gemcitabine)

IT 95058-81-4, Gemcitabine **149606-27-9, Auristatin-PE**
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(induction of growth inhibition and apoptosis in pancreatic cancer cells by **auristatin-PE** and gemcitabine)

RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD

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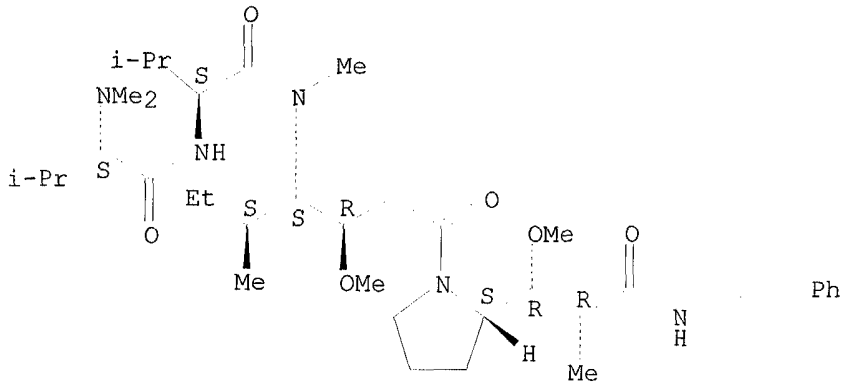
IT **149606-27-9, Auristatin-PE**
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(induction of growth inhibition and apoptosis in pancreatic cancer cells by **auristatin-PE** and gemcitabine)

RN 149606-27-9 HCAPLUS

CN L-Valinamide, N,N-dimethyl-L-valyl-N-[(1S,2R)-2-methoxy-4-[(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-[(2-phenylethyl)amino]propyl]-1-pyrrolidinyl]-1-[(1S)-1-methylpropyl]-4-oxobutyl]-N-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L30 ANSWER 10 OF 20 HCAPLUS COPYRIGHT 2003 ACS on STN
AN 1998:361435 HCAPLUS
DN 129:144546
ED Entered STN: 15 Jun 1998
TI Antineoplastic agents 365. Dolastatin 10 SAR probes
AU Pettit, George R.; Srirangam, Jayaram K.; Barkoczy, Jozsef; Williams, Michael D.; Boyd, Michael R.; Hamel, Ernest; Pettit, Robin K.; Hogan, Fiona; Bai, Ruoli; Chapuis, Jean-Charles; McAllister, Shane C.; Schmidt, Jean M.

CS Cancer Research Inst. & Dep. Chem., Arizona State Univ., Tempe, AZ, 872404, USA
SO Anti-Cancer Drug Design (**1998**), 13(4), 243-277
CODEN: ACDDEA; ISSN: 0266-9536
PB Oxford University Press
DT Journal
LA English
CC 1-3 (Pharmacology)
Section cross-reference(s): 34
AB Thirty-eight new structural modifications of dolastatin 10 were synthesized and evaluated against a variety of human and murine cancer cell lines, and for their ability to inhibit tubulin polymerization and vinblastine and GTP binding to tubulin. Dolastatin 10 and one structural modification had antifungal activity, while one other structural modification exhibited antibacterial activity. Some of the new peptides approximated the antineoplastic potency of dolastatin 10, especially those based on replacement of the Doe (dolaphenine) unit with Met, Phe or an appropriately substituted phenylethylamide.
ST dolastatin analog prepn anticancer SAR
IT Structure-activity relationship
(antitumor; preparation and anticancer SAR of dolastatin 10 analogs)
IT Antibacterial agents
(dolastatin 10 analogs)
IT Fungicides
(dolastatin 10 and analogs)
IT Tubulins
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(polymerization; preparation and anticancer SAR of dolastatin 10 analogs)
IT 110417-88-4, Dolastatin 10
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(analogs; preparation and anticancer SAR of)
IT 148692-26-6P 159255-75-1P 160800-49-7P 160800-51-1P 160800-54-4P
160800-55-5P 160800-56-6P 160800-57-7P 160868-07-5P 160868-08-6P
161485-77-4P 161485-78-5P 161485-79-6P 161485-81-0P,
Auristatin M 176307-03-2P 176307-04-3P 176307-05-4P
176307-17-8P 176307-18-9P 176307-19-0P 176307-20-3P 176307-21-4P
176307-22-5P 176307-23-6P 176307-24-7P 176307-25-8P 176307-26-9P
179040-06-3P 179040-07-4P 179040-08-5P 179040-09-6P 179040-10-9P
179040-11-0P 179040-12-1P 203006-92-2P 210898-16-1P 210898-41-2P
210898-46-7P 210898-49-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and anticancer SAR of dolastatin 10 analogs)
IT 64-04-0, Phenethylamine 95-51-2, 2-Chloroaniline 106-47-8, 4-Chloroaniline, reactions 108-42-9, 3-Chloroaniline 136-95-8, 2-Benzothiazolamine 580-17-6, 3-Quinolinamine 1099-45-2 2488-15-5, N-tert-Butoxycarbonyl-L-methionine 2491-18-1, L-Methionine methyl ester hydrochloride 5717-37-3 13734-34-4, N-Boc-L-phenylalanine 15761-39-4, Boc-L-proline 69610-41-9, Boc-prolinal 120205-50-7, N-Boc-dolaproine 120205-52-9 120205-53-0 149606-89-3 161857-47-2 174136-55-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation and anticancer SAR of dolastatin 10 analogs)
IT 65595-02-0P 92122-49-1P 104700-41-6P 126424-82-6P 133120-89-5P
160800-58-8P 160800-60-2P 160800-62-4P 160800-63-5P 160800-64-6P
160800-65-7P 160868-09-7P 160868-10-0P 161485-82-1P 161485-83-2P
161485-84-3P 161485-86-5P 176307-06-5P 176307-07-6P 176307-08-7P
176307-27-0P 179039-97-5P 179039-98-6P 179039-99-7P 179040-00-7P
179040-01-8P 179040-13-2P 179040-15-4P 179040-16-5P 179667-84-6P
179667-86-8P 179667-87-9P 179667-88-0P 179667-95-9P 179667-96-0P

179667-98-2P 179668-03-2P 179668-05-4P 179668-06-5P 179668-07-6P
179668-14-5P 179668-15-6P 179668-17-8P 210899-08-4P 210899-15-3P
210899-17-5P 210899-19-7P 210899-21-1P 210899-40-4P 210899-42-6P
210899-44-8P 210899-46-0P 210899-48-2P 210899-49-3P 210899-51-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and anticancer SAR of dolastatin 10 analogs)
IT 86-01-1, 5'-GTP 865-21-4, Vinblastine
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(tubulin binding; preparation and anticancer SAR of dolastatin 10 analogs)
RE.CNT 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD
RE
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L30 ANSWER 11 OF 20 HCAPLUS COPYRIGHT 2003 ACS on STN
AN 1998:328201 HCAPLUS
DN 129:103877
ED Entered STN: 03 Jun 1998
TI Successful treatment of human chronic lymphocytic leukemia xenografts with combination biological agents **auristatin PE** and bryostatin 1
AU Mohammad, Ramzi M.; Varterasian, Mary L.; Almatchy, Victor P.; Hannoudi, Ghadeer N.; Pettit, George R.; Al-Katib, Ayad
CS Division of Hematology and Oncology, Department of Internal Medicine, Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, MI, 48201, USA
SO Clinical Cancer Research (**1998**), 4(5), 1337-1343
CODEN: CCREF4; ISSN: 1078-0432
PB American Association for Cancer Research
DT Journal
LA English
CC 1-6 (Pharmacology)
AB We tested the activity of dolastatin 10 (a natural product derived from the shell-less marine mollusk, Dolabella auricularia, a sea hare) and its structural modification, **auristatin PE**, alone and in combination with bryostatin 1 (a protein kinase C activator derived from the marine bryozoan Bugula neritina) on a human B-cell chronic lymphocytic leukemia cell line (WSU-CLL) and in a severe combined immune deficient (SCID) mouse xenograft model bearing this cell line. WSU-CLL cells were cultured in RPMI 1640 at a concentration of 2 + 105/mL using a 24-well plate. Agents were added to triplicate wells, and cell count, viability, mitosis, and apoptosis were assessed after 24 h of incubation at 37°C. Results showed that dolastatin 10 had no apparent inhibition of cell growth at concns. less than 500 pg/mL. **Auristatin**

PE, on the other hand, showed significant growth inhibition at concns. as low as 50 pg/mL. **Auristatin PE**-treated cultures, at this concentration, exhibited 27 and 4.5% mitosis and apoptosis, resp. Dolastatin 10, at the same concentration, did not exert any effect and was comparable with that of control cultures. In the WSU-CLL-SCID mouse xenograft model, the efficacy of these agents alone and in combination with bryostatin 1 was evaluated. Tumor growth inhibition (T/C), tumor growth delay (T-C), and log10 kill for dolastatin 10, **auristatin PE**, and bryostatin 1 were 14%, 25 days, and 1.98; 2%, 25 days, and 1.98; 19%, 13 days, and 1.03, resp. **Auristatin-PE** produced cure in three of five mice, whereas dolastatin 10 showed activity but no cures. When given in combination, **auristatin PE** + bryostatin 1-treated animals were all free of tumors (five of five) for 150 days and were considered cured. Dolastatin 10 + bryostatin 1-treated animals produced cure in only two of five mice. We conclude that: (a) **auristatin-PE** is more effective in this model than dolastatin 10; (b) **auristatin PE** can be administered at a concentration 10 times greater than dolastatin 10; (c) there is a synergetic effect between these agents and bryostatin 1, which is more apparent in the bryostatin 1 + **auristatin PE** combination. The use of these agents should be explored clin. in the treatment of CLL.

ST leukemia antitumor **auristatin PE** bryostatin

IT **Antitumor agents**
(leukemia; leukemia inhibition by **auristatin PE** and bryostatin 1)

IT Drug interactions
(synergistic; leukemia inhibition by **auristatin PE** and bryostatin 1)

IT 83314-01-6, Bryostatin 1 110417-88-4, Dolastatin 10 **149606-27-9**, **Auristatin PE**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(leukemia inhibition by **auristatin PE** and bryostatin 1)

RE.CNT 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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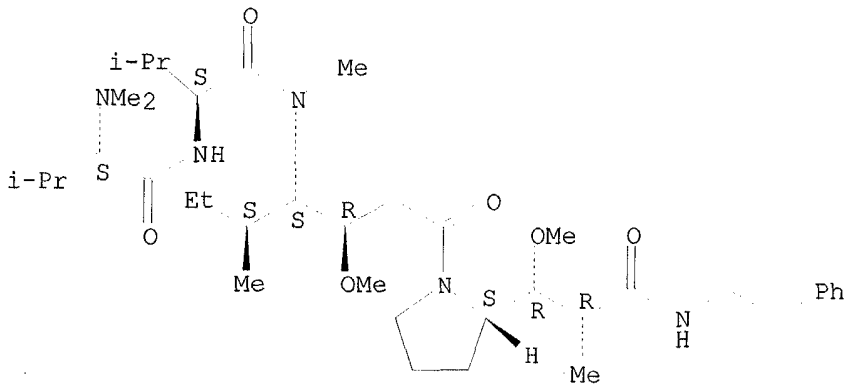
IT **149606-27-9, Auristatin PE**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(leukemia inhibition by **auristatin PE** and bryostatin 1)

RN 149606-27-9 HCAPLUS
CN L-Valinamide, N,N-dimethyl-L-valyl-N-[(1S,2R)-2-methoxy-4-[(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-[(2-phenylethyl)amino]propyl]-1-pyrrolidinyl]-1-[(1S)-1-methylpropyl]-4-oxobutyl]-N-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L30 ANSWER 12 OF 20 HCAPLUS COPYRIGHT 2003 ACS on STN
AN 1998:158342 HCAPLUS
DN 128:278710
ED Entered STN: 18 Mar 1998
TI Synergistic interaction of selected marine animal anticancer drugs against human diffuse large cell lymphoma
AU Mohammad, Ramzi M.; Pettit, George R.; Almatchy, Victor P.; Wall, Nathan; Varterasian, Mary; Al-Katib, Ayad
CS Division of Hematology and Oncology, Department of Internal Medicine, Wayne State University School of Medicine, Detroit, MI, 48201, USA
SO Anti-Cancer Drugs (**1998**), 9(2), 149-156
CODEN: ANTDEV; ISSN: 0959-4973
PB Rapid Science Ltd.
DT Journal
LA English
CC 1-6 (Pharmacology)
AB We studied the antitumor effects of dolastatin 10, its structural modification, **auristatin PE** (**TZT-1027**), and vincristine alone and in combination with bryostatin 1 on a human diffuse large cell lymphoma line (WSU-DLCL2) in vitro and in vivo. WSU-DLCL2 cells were cultured in RPMI 1640 at a concentration of 2 x 105/mL using a 24-well plate. Agents were added to triplicate wells, and cell count, viability, mitosis and apoptosis were assessed. Dolastatin 10 showed no apparent inhibition of cell growth at concns. less than 500 pg/mL. **Auristatin PE** showed significant growth inhibition at concns. as low as 10 pg/mL, while vincristine had a minimal effect at 50 pg/mL. Dolastatin 10, **auristatin PE** and vincristine-treated cultures, at 50 pg/mL, exhibited 11, 1.7; 45, 11.8%; and 39, 25% mitosis and apoptosis, resp. In the WSU-DLCL2 SCID mouse xenograft model, the efficacy of these agents alone or in combination with

bryostatin 1 was evaluated. Tumor growth inhibition (T/C), tumor growth delay (T-C) and log10 kill for dolastatin 10, **auristatin PE**, vincristine and bryostatin 1 were 30%, 14 days and 1.4; 0.0%, 55 days and 5.5; 29.6%, 16 days and 1.6; and 39%, 7 days and 0.7, resp. When given in combination, two out of five mice treated with **auristatin PE** + bryostatin 1 were free of tumors for 150 days and were considered cured. Dolastatin 10 + bryostatin 1 and vincristine + bryostatin 1 combinations were highly active but no cure was observed We conclude that: (i) **auristatin PE** is more effective in this model than dolastatin 10, vincristine or bryostatin 1, (ii) **auristatin PE** can be administered at a concentration 10 times greater than dolastatin 10, and (iii) there is a synergistic effect between these agents and bryostatin 1, which is more apparent in the bryostatin 1 + **auristatin PE** combination. The use of these agents should be further explored clin. in the treatment of lymphoma.

ST marine animal product anticancer synergistic interaction; dolastatin 10 lymphoma inhibitor; **TZT 1027** lymphoma inhibitor; bryostatin 1 lymphoma inhibitor; vincristine lymphoma inhibitor

IT **Antitumor agents**
(lymphoma; synergistic interaction of selected marine animal anticancer drugs against human diffuse large cell lymphoma)

IT Marine animal
(synergistic interaction of selected marine animal anticancer drugs against human diffuse large cell lymphoma)

IT Drug interactions
(synergistic; synergistic interaction of selected marine animal anticancer drugs against human diffuse large cell lymphoma)

IT 57-22-7, Vincristine 83314-01-6, Bryostatin 1 110417-88-4, Dolastatin 10 **149606-27-9, TZT-1027**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synergistic interaction of selected marine animal anticancer drugs against human diffuse large cell lymphoma)

RE.CNT 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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(2) Al-Katib, A; J Immunother 1993, V14, P33 HCAPLUS
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(16) Mohammad, R; Leuk Res 1993, V17, P1 HCAPLUS
(17) Mohammad, R; Leuk Res 1995, V19, P667 HCAPLUS
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(19) Pettit, G; J Am Chem Soc 1982, V104, P6846 HCAPLUS
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(21) Pettit, G; Progress in the chemistry of organic natural products 1991, P154
(22) Pettit, G; Progress in the chemistry of organic natural products 1997, P2

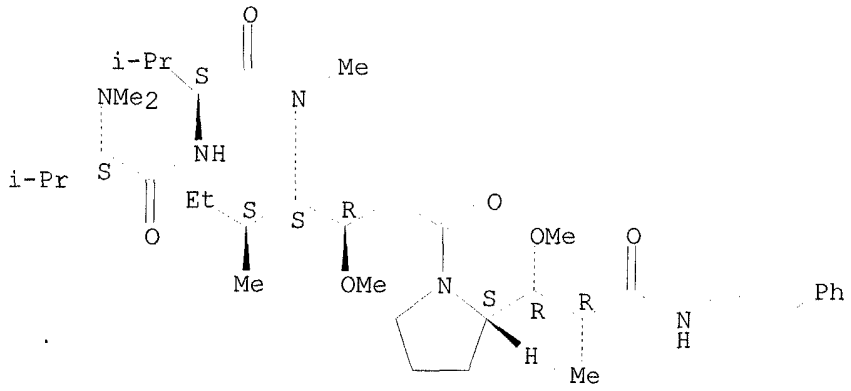
IT **149606-27-9, TZT-1027**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synergistic interaction of selected marine animal anticancer drugs against human diffuse large cell lymphoma)

RN 149606-27-9 HCAPLUS

CN L-Valinamide, N,N-dimethyl-L-valyl-N-[(1S,2R)-2-methoxy-4-[(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-[(2-phenylethyl)amino]propyl]-1-pyrrolidinyl]-1-[(1S)-1-methylpropyl]-4-oxobutyl]-N-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L30 ANSWER 13 OF 20 HCAPLUS COPYRIGHT 2003 ACS on STN

AN 1997:222017 HCAPLUS

DN 126:301480

ED Entered STN: 05 Apr 1997

TI Antitumor activity of **TZT-1027**, a novel dolastatin 10 derivative

AU Kobayashi, Motohiro; Natsume, Tsugitaka; Tamaoki, Satoru; **Watanabe, Jun-Ichi**; Asano, Hajime; Mikami, Takashi; Miyasaka, Katsuhiko; Miyazaki, Koichi; Gondo, Masaaki

CS Pharmacological Research Department, **Teikoku** Hormone Mfg. Co., Ltd., Kawasaki, 213, Japan

SO Japanese Journal of Cancer Research (**1997**), 88(3), 316-327
CODEN: JJCREP; ISSN: 0910-5050

PB Japanese Cancer Association

DT Journal

LA English

CC 1-6 (Pharmacology)

AB Dolastatin 10, a pentapeptide isolated from the marine mollusk Dolabella auricularia, has antitumor activity. **TZT-1027**, a dolastatin 10 derivative, is a newly synthesized antitumor compound The authors evaluated its antitumor activity against a variety of transplantable tumors in mice. Intermittent injections of **TZT-1027** were more effective than single or repeated injections in mice with P388 leukemia and B16 melanoma. Consequently, **TZT-1027** shows schedule dependency. **TZT-1027** was effective against P388 leukemia not only when administered i.p., but also when given i.v. However, although **TZT-1027** given i.v. was active against murine solid tumors, **TZT-1027** administered i.p. was ineffective against all the tumors tested with the exception of colon 26 adenocarcinoma. The i.v. injection of **TZT-1027** at a dose of 2.0 mg/kg remarkably inhibited the growth of three murine solid tumors; colon 26 adenocarcinoma, B16 melanoma and M5076 sarcoma, with T/C values of less than 6%. The antitumor activities of **TZT -1027** against these tumors were superior or comparable to those

of the reference agents; dolastatin 10, cisplatin, vincristine, 5-fluorouracil (5-FU) and E7010. In expts. with drug-resistant P388 leukemia, **TZT-1027** showed good activity against cisplatin-resistant P388 and moderate activity against vincristine- and 5-fluorouracil-resistant P388, but no activity against adriamycin-resistant P388. **TZT-1027** was also effective against human xenografts, i.e., tumor regression was observed in mice bearing MX-1 breast and LX-1 lung carcinomas. **TZT-1027** at 10μM almost completely inhibited the assembly of porcine brain microtubules. Therefore, its mechanism of antitumor action seems to be, at least in part, ascribable to the inhibition of microtubule assembly. Because of its good preclin. activity, **TZT-1027** has been entered into phase I clin. trials.

ST antitumor **TZT 1027** dolastatin 10 deriv

IT **Antitumor agents**
(adenocarcinoma, colon 26; antitumor activity of novel dolastatin 10 derivative in animal and human various cell lines)

IT Animal cell line
Antitumor agents
Microtubule
(antitumor activity of novel dolastatin 10 derivative in animal and human various cell lines)

IT Lung, neoplasm
Mammary gland
(carcinoma, inhibitors; antitumor activity of novel dolastatin 10 derivative in animal and human various cell lines)

IT **Antitumor agents**
(leukemia, P388; antitumor activity of novel dolastatin 10 derivative in animal and human various cell lines)

IT **Antitumor agents**
(lung carcinoma; antitumor activity of novel dolastatin 10 derivative in animal and human various cell lines)

IT **Antitumor agents**
(mammary gland carcinoma; antitumor activity of novel dolastatin 10 derivative in animal and human various cell lines)

IT **Antitumor agents**
(melanoma, B16; antitumor activity of novel dolastatin 10 derivative in animal and human various cell lines)

IT **Antitumor agents**
(sarcoma, M5076; antitumor activity of novel dolastatin 10 derivative in animal and human various cell lines)

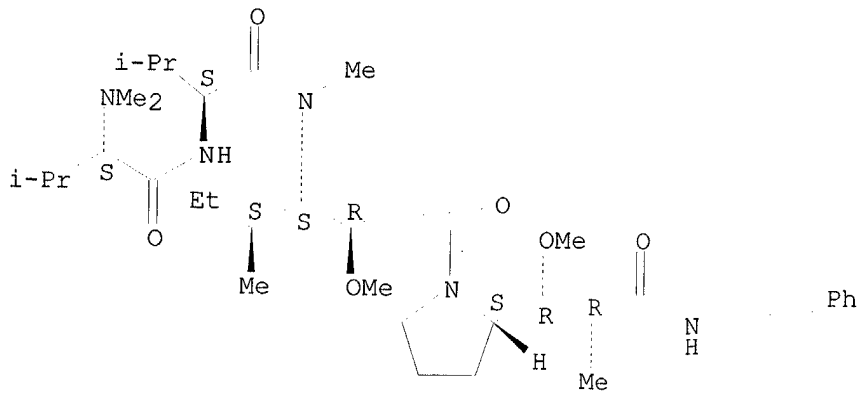
IT 51-21-8, 5-Fluorouracil 57-22-7, Vincristine 15663-27-1, Cisplatin 110417-88-4, Dolastatin 10 141430-65-1, Benzenesulfonamide, N-[2-[(4-hydroxyphenyl)amino]-3-pyridinyl]-4-methoxy- **149606-27-9**, **TZT-1027**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antitumor activity of novel dolastatin 10 derivative in animal and human various cell lines)

IT **149606-27-9, TZT-1027**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antitumor activity of novel dolastatin 10 derivative in animal and human various cell lines)

RN 149606-27-9 HCAPLUS

CN L-Valinamide, N,N-dimethyl-L-valyl-N-[(1S,2R)-2-methoxy-4-[(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-[(2-phenylethyl)amino]propyl]-1-pyrrolidinyl]-1-[(1S)-1-methylpropyl]-4-oxobutyl]-N-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



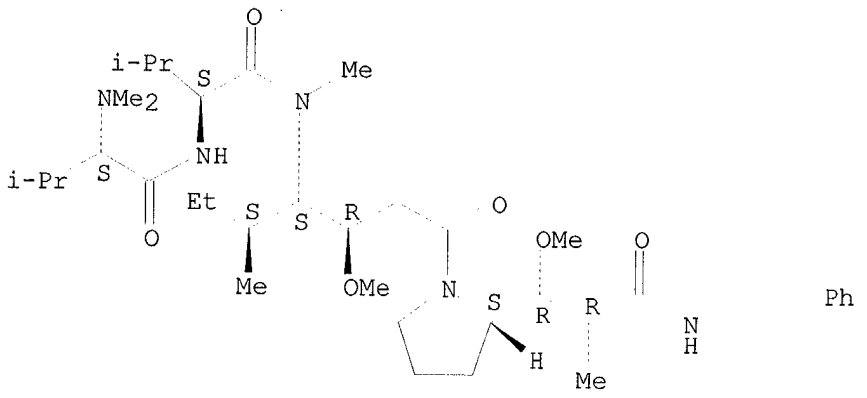
L30 ANSWER 14 OF 20 HCAPLUS COPYRIGHT 2003 ACS on STN
AN 1996:305553 HCAPLUS
DN 125:25736
ED Entered STN: 24 May 1996
TI A novel antitumor agent **TZT-1027**, dolastatin 10 derivative
AU Sakakibara, K.; Kobayashi, M.; Miyazaki, K.; Gondo, M.; Mikami, T.; Tsukagoshi, S.
CS Organic Chemistry Research Department, **Teikoku** Hormone Mfg. Co. Ltd., Kawasaki, Japan
SO Proceedings of the International Cancer Congress, Free Papers and Posters, 16th, New Delhi, Oct. 30-Nov. 5, 1994 (**1994**), Volume 4, 2905-2908. Editor(s): Rao, R. S. Publisher: Monduzzi Editore, Bologna, Italy.
CODEN: 62UYAO
DT Conference
LA English
CC 1-6 (Pharmacology)
AB We studied the antitumor activity of newly synthesized dolastatin 10 derivs. using an i.p.-i.p. P388 leukemia model. As a result, we found TZT-0006, TZT-1019 and **TZT-1027** to possess superior antitumor activity. In particular, **TZT-1027** showed remarkable activities against several murine tumors following its i.v. administration. **TZT-1027** was further examined for the administration schedule-dependency using P388 leukemia and B16 melanoma, and the effect on the assembly of rat brain microtubules. The results indicate that its antitumor activity is schedule-dependent and, in part, ascribed to the inhibition of microtubule assembly. This study suggests that **TZT-1027** is a promising antitumor agent.
ST neoplasm inhibitor **TZT 1027** 1019 0006; dolastatin 10 deriv neoplasm inhibitor
IT **Neoplasm inhibitors**
(antitumor activities of dolastatin 10 and derivs. **TZT-1027**, TZT-1019, and TZT-0006)
IT Microtubule
(inhibition of microtubule assembly; antitumor activities of dolastatin 10 and derivs. **TZT-1027**, TZT-1019, and TZT-0006)
IT 110417-88-4, Dolastatin 10 149606-04-2, TZT 0006 **149606-27-9, TZT 1027** 159255-70-6, TZT 1019
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antitumor activities of dolastatin 10 and derivs. **TZT-1027**, TZT-1019, and TZT-0006)
IT **149606-27-9, TZT 1027**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antitumor activities of dolastatin 10 and derivs. **TZT-1027**, TZT-1019, and TZT-0006)

RN 149606-27-9 HCAPLUS

CN L-Valinamide, N,N-dimethyl-L-valyl-N-[(1S,2R)-2-methoxy-4-[(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-[(2-phenylethyl)amino]propyl]-1-pyrrolidinyl]-1-[(1S)-1-methylpropyl]-4-oxobutyl]-N-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L30 ANSWER 15 OF 20 HCAPLUS COPYRIGHT 2003 ACS on STN

AN 1995:1005887 HCAPLUS

DN 124:203030

ED Entered STN: 29 Dec 1995

TI Antineoplastic agents. 337. Synthesis of dolastatin 10 structural modifications

AU Pettit, George R.; Srirangam, Jayaram K.; Barkoczy, Jozsef; Williams, Michael D.; Durkin, Kieran P. M.; Boyd, Michael R.; Bai, Ruoli; Hamel, Ernest; Schmidt, Jean M.; Chapius, Jean-Charles

CS Dep. Chem., Arizona State Univ., Tempe, AZ, 85287-16-4, USA

SO Anti-Cancer Drug Design (**1995**), 10(7), 529-44
CODEN: ACDDEA; ISSN: 0266-9536

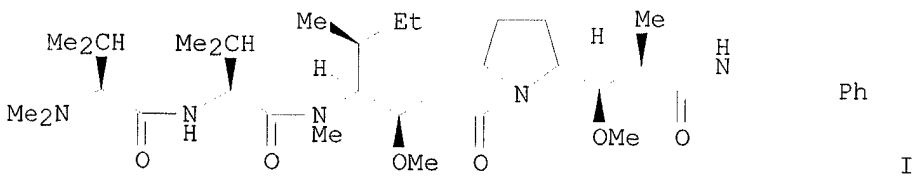
PB Oxford University Press

DT Journal

LA English

CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1

GI



I

AB New structural modifications of the marine mollusk peptide constituent dolastatin 10 have been synthesized and evaluated against a variety of cancer cell lines and for their ability to inhibit tubulin polymerization A number of useful structure-activity relationships were uncovered. The most important observation was that the dolaphenine unit of dolastatin 10 could

be satisfactorily replaced with a phenethylamine. Peptide I, designated **auristatin PE**, was found to exhibit inhibition of cancer cell growth and tubulin assembly comparable to that of dolastatin 10.

ST antitumor structure activity dolastatin 10; **auristatin PE** prepn neoplasm inhibitor

IT **Neoplasm inhibitors**
(preparation and antitumor activity of dolastatin 10 analogs)

IT Molecular structure-biological activity relationship
(neoplasm-inhibiting, preparation and antitumor activity of dolastatin 10 analogs)

IT 110417-88-4DP, Dolastatin 10, analogs 133120-90-8P 149606-12-2P
149606-27-9P, Auristatin PE 149606-28-0P
149606-29-1P 149632-85-9P 160800-50-0P 160800-52-2P 160800-53-3P
174136-58-4P 174136-59-5P 174136-60-8P 174136-61-9P 174136-62-0P
174136-63-1P 174136-64-2P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and antitumor activity of dolastatin 10 analogs)

IT 62-53-3, Benzenamine, reactions 64-04-0, Phenethylamine 100-46-9, Benzylamine, reactions 107-20-0, α-Chloroacetaldehyde 405-39-0
1583-88-6, p-Fluorophenethylamine 2018-66-8 2038-57-5,
3-Phenylpropylamine 2491-18-1, Methionine methyl ester hydrochloride
2812-32-0 3160-59-6 18684-16-7, Histidine methyl ester hydrochloride
20888-05-5 24954-67-4, 4-Nitrophenethylamine 27894-50-4 52396-85-7
73918-56-6, p-Bromophenethylamine 99281-95-5 120205-48-3 120205-50-7
120205-52-9 120205-54-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation and antitumor activity of dolastatin 10 analogs)

IT 133565-36-3P 149606-56-4P 149606-70-2P 149606-90-6P 149606-91-7P
149606-92-8P 160800-59-9P 160800-61-3P 160800-84-0P 161485-86-5P
174136-49-3P 174136-50-6P 174136-52-8P 174136-53-9P 174136-54-0P
174136-55-1P 174136-56-2P 174136-57-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and antitumor activity of dolastatin 10 analogs)

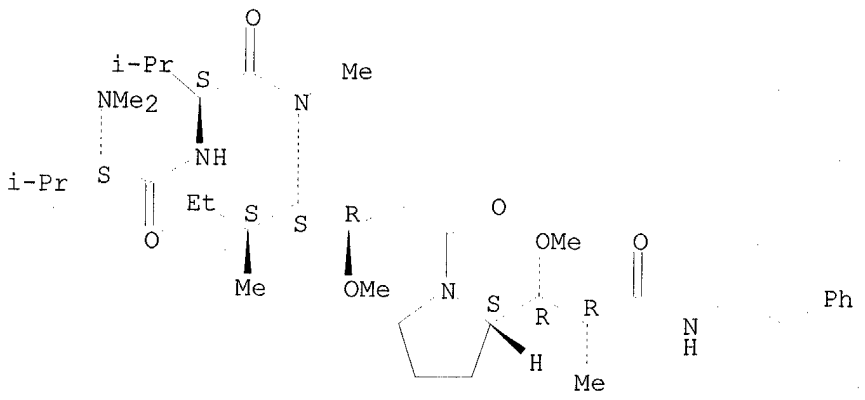
IT 174136-51-7P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation and antitumor activity of dolastatin 10 analogs)

IT **149606-27-9P, Auristatin PE**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and antitumor activity of dolastatin 10 analogs)

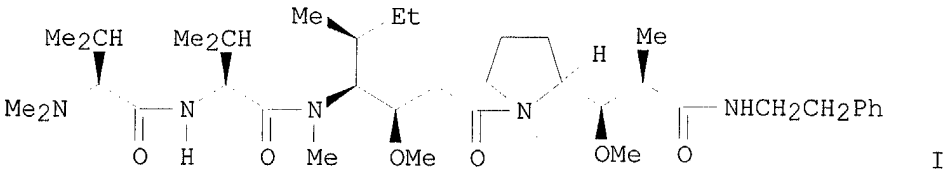
RN 149606-27-9 HCAPLUS

CN L-Valinamide, N,N-dimethyl-L-valyl-N-[(1S,2R)-2-methoxy-4-[(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-[(2-phenylethyl)amino]propyl]-1-pyrrolidinyl]-1-[(1S)-1-methylpropyl]-4-oxobutyl]-N-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L30 ANSWER 16 OF 20 HCAPLUS COPYRIGHT 2003 ACS on STN
AN 1995:959434 HCAPLUS
DN 124:176876
ED Entered STN: 02 Dec 1995
TI Synthesis and antitumor activity of novel dolastatin 10 analogs
AU Miyazaki, Koichi; Kobayashi, Motohiro; Natsume, Tsugitaka; Gondo, Masaaki; Mikami, Takashi; Sakakibara, Kyoichi; Tsukagoshi, Shigeru
CS Res. Dep., **Teikoku** Hormone Mfg. Co., Ltd., Kawasaki, 213, Japan
SO Chemical & Pharmaceutical Bulletin (**1995**), 43(10), 1706-18
CODEN: CPBTAL; ISSN: 0009-2363
PB Pharmaceutical Society of Japan
DT Journal
LA English
CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1
GI



I

AB Novel analogs of dolastatin 10, a a potent antineoplastic pentapeptide, each modified at one of the constituent amino acid derivs., were synthesized and their antitumor activity was evaluated against P388 leukemia in mice. The structural requirements for antitumor activity are discussed. Some of the analogs showed excellent activity in vivo. Highly active analog I, which lacks the thiazole group of dolastatin 10, was selected for further development as an antitumor agent.
ST antineoplastic structure activity dolastatin analog; antitumor dolastatin 10 analog prepn
IT **Neoplasm inhibitors**
(synthesis and antitumor activity of novel dolastatin 10 analogs)
IT Molecular structure-biological activity relationship
(neoplasm-inhibiting, synthesis and antitumor activity of novel dolastatin 10 analogs)
IT 110417-88-4DP, Dolastatin 10, analogs 130272-92-3P 130272-98-9P
149606-04-2P 149606-05-3P 149606-06-4P 149606-07-5P 149606-08-6P
149606-12-2P 149606-13-3P 149606-14-4P 149606-15-5P 149606-16-6P
149606-27-9P 149606-28-0P 149606-29-1P 149632-83-7P

149632-85-9P 159255-63-7P 159255-64-8P 159255-65-9P 159255-66-0P
159255-67-1P 159255-68-2P 159255-69-3P 173441-21-9P 173441-26-4P
173653-51-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(synthesis and antitumor activity of novel dolastatin 10 analogs)

IT 60-23-1, 2-Aminoethanethiol 62-53-3, Benzenamine, reactions 64-04-0, 2-Phenylethylamine 100-46-9, Benzylamine, reactions 122-63-4, Benzyl propionate 140-11-4, Benzyl acetate 503-74-2, Isovaleric acid 1118-68-9, N,N-Dimethylglycine 1142-20-7 1149-26-4 2018-66-8 2038-57-5, 3-Phenylpropylamine 2812-31-9, N,N-Dimethylalanine 2812-32-0 3160-59-6 17407-55-5 21691-44-1 38330-80-2, Methyl potassium malonate 42417-65-2, N-Benzyloxycarbonyl-N-methylvaline 69610-41-9, N-tert-Butoxycarbonyl-L-prolinal 79069-50-4, N-tert-Butoxycarbonyl-L-alaninal 120205-52-9 120205-53-0 120205-54-1 130199-66-5 135383-55-0
RL: RCT (Reactant); RACT (Reactant or reagent)
(synthesis and antitumor activity of novel dolastatin 10 analogs)

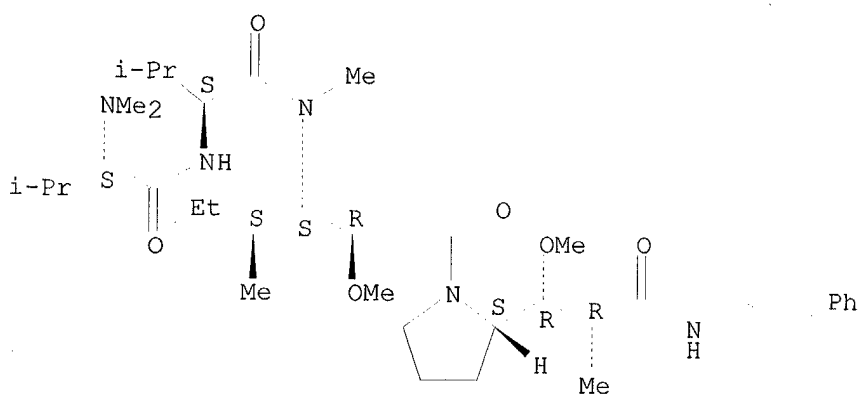
IT 108910-03-8P 119960-01-9P 120021-36-5P 120205-58-5P 148565-06-4P
149606-38-2P 149606-39-3P 149606-40-6P 149606-41-7P 149606-42-8P
149606-45-1P 149606-46-2P 149606-47-3P 149606-48-4P 149606-49-5P
149606-51-9P 149606-52-0P 149606-54-2P 149606-55-3P 149606-56-4P
149606-57-5P 149606-59-7P 149606-61-1P 149606-62-2P 149606-63-3P
149606-64-4P 149606-65-5P 149606-68-8P 149606-69-9P 149606-70-2P
149606-71-3P 149606-72-4P 149606-74-6P 149606-75-7P 149606-97-3P
154633-73-5P 157967-03-8P 163768-51-2P 163768-52-3P 173441-03-7P
173441-04-8P 173441-05-9P 173441-06-0P 173441-07-1P 173441-08-2P
173441-09-3P 173441-10-6P 173441-11-7P 173441-12-8P 173441-13-9P
173441-14-0P 173441-15-1P 173441-16-2P 173441-17-3P 173441-18-4P
173441-19-5P 173441-20-8P 173441-22-0P 173441-23-1P 173441-24-2P
173441-25-3P 173441-27-5P 173441-28-6P 173653-47-9P 173653-48-0P
173653-49-1P 173653-50-4P 173653-52-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(synthesis and antitumor activity of novel dolastatin 10 analogs)

IT 120205-49-4P 133565-38-5P 148616-84-6P
RL: SPN (Synthetic preparation); PREP (Preparation)
(synthesis and antitumor activity of novel dolastatin 10 analogs)

IT **149606-27-9P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(synthesis and antitumor activity of novel dolastatin 10 analogs)

RN 149606-27-9 HCAPLUS
CN L-Valinamide, N,N-dimethyl-L-valyl-N-[(1S,2R)-2-methoxy-4-[(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-[(2-phenylethyl)amino]propyl]-1-pyrrolidinyl]-1-[(1S)-1-methylpropyl]-4-oxobutyl]-N-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L30 ANSWER 17 OF 20 HCAPLUS COPYRIGHT 2003 ACS on STN
AN 1995:435632 HCAPLUS
DN 122:214533
ED Entered STN: 23 Mar 1995
TI Preparation of tetrapeptide amide derivatives, dolastatin 10 analogs, as anticancer and antitumor agents
IN Sakakibara, Kyoichi; Gondo, Masaaki; Myazaki, Koichi
PA **Teikoku Hormone Mfg Co Ltd, Japan**
SO Jpn. Kokai Tokkyo Koho, 15 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
IC ICM C07K005-06
ICA A61K037-02
CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI JP 06234790	A2	19940823	JP 1993-43323	19930209 <--
PRAI JP 1993-43323		19930209 <--		

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Tetrapeptides (I; R1 = R2 = R3 = iso-Pr; R1 = H, R2 = iso-Pr, R3 = sec-Bu; R1 = iso-Bu, R2 = R3 = sec-Bu; R1 = me, R2 = iso-Pr, R3 = sec-Bu), having cell proliferation-inhibiting and/or antineoplastic activity more potent than that of dolastatin 10 (no data), are prepared Thus, Z-Val-OH was treated with carbonyldiimidazole in THF and reacted under ice-cooling for 6 h with a reaction mixture obtained by heating malonic acid monomethyl ester K salt with MgCl2 in THF at 55° for 6 h to give valine derivative (II). II was reduced by NaBH4 in MeOH to an alc. (III; R = H, R1 = Z, R2 = Me) and methylated by MeI and Ag2O in DMF to give III (R = R2 = Me, R1 = Z) which was converted into tripeptide derivative III (R = Me, R1 = Q, R2 = tert-butyl). The latter tripeptide derivative was deprotected with CF3CO2H in CH2Cl2 and condensed with amide (IV.HCl) (preparation given) by using (EtO)2P(O)CN and Et3N in DMF to give title compound (V). A total of 4 I were prepared
ST tetrapeptide amide prepn anticancer antitumor; dolastatin 10 analog prepn anticancer antitumor
IT **Neoplasm inhibitors**

(preparation of tetrapeptide amide derivs. (dolastatin 10 analogs) as anticancer and antitumor agents)

IT Peptides, preparation
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(tetra-, amides, preparation of tetrapeptide amide derivs. (dolastatin 10 analogs) as anticancer and antitumor agents)

IT 64-04-0, Phenethylamine
RL: RCT (Reactant); RACT (Reactant or reagent)
(amidation with pyrrolidinylmethoxymethylpropionic acid derivative in preparation of tetrapeptide amide derivs. (dolastatin 10 analogs) as anticancer and antitumor agents)

IT 2812-32-0, N,N-Dimethyl-L-valine
RL: RCT (Reactant); RACT (Reactant or reagent)
(condensation with divaline derivative in preparation of tetrapeptide amide derivs. (dolastatin 10 analogs) as anticancer and antitumor agents)

IT 1149-26-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(condensation with malonic acid monomethyl ester K salt in preparation of tetrapeptide amide derivs. (dolastatin 10 analogs) as anticancer and antitumor agents)

IT 38330-80-2, Malonic acid monomethyl ester potassium salt
RL: RCT (Reactant); RACT (Reactant or reagent)
(condensation with valine derivative in preparation of tetrapeptide amide derivs. (dolastatin 10 analogs) as anticancer and antitumor agents)

IT 115-11-7, Isobutene, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(esterification with aminohydroxyisoheptanoic acid derivative in preparation of
tetrapeptide amide derivs. (dolastatin 10 analogs) as anticancer and antitumor agents)

IT 149606-97-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(hydrogenolysis in preparation of tetrapeptide amide derivs. (dolastatin 10 analogs) as anticancer and antitumor agents)

IT 120205-50-7P 120205-52-9P 120205-58-5P 147778-59-4P 149606-39-3P
149606-41-7P 149606-47-3P 149606-52-0P 149606-56-4P 149606-61-1P
149606-64-4P 149606-68-8P 149606-70-2P 149606-89-3P 149632-87-1P
149632-88-2P 149664-79-9P 161712-03-4P 161712-04-5P 161712-06-7P
161814-03-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate for preparation of tetrapeptide amide derivs. (dolastatin 10 analogs) as anticancer and antitumor agents)

IT 74-88-4, Methyl iodide, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(methylation of aminohydroxyisoheptanoic acid derivative in preparation of tetrapeptide amide derivs. (dolastatin 10 analogs) as anticancer and antitumor agents)

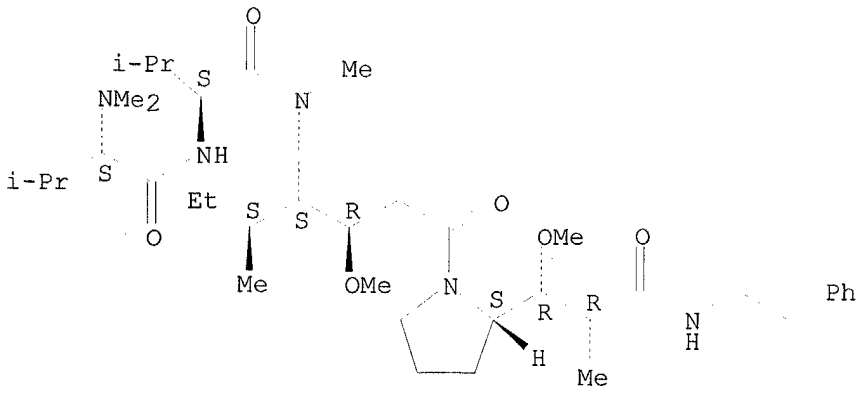
IT **149606-27-9P** 159255-77-3P 161712-01-2P 161712-02-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of tetrapeptide amide derivs. (dolastatin 10 analogs) as anticancer and antitumor agents)

IT **149606-27-9P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of tetrapeptide amide derivs. (dolastatin 10 analogs) as anticancer and antitumor agents)

RN 149606-27-9 HCAPLUS

CN L-Valinamide, N,N-dimethyl-L-valyl-N-[(1S,2R)-2-methoxy-4-[(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-[(2-phenylethyl)amino]propyl]-1-pyrrolidinyl]-1-[(1S)-1-methylpropyl]-4-oxobutyl]-N-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L30 ANSWER 18 OF 20 HCAPLUS COPYRIGHT 2003 ACS on STN
AN 1995:234566 HCAPLUS
DN 122:10688
ED Entered STN: 10 Dec 1994
TI The elucidation and synthesis of antineoplastic tetrapeptide phenethylamides analogs of dolastatin 10.
IN Petit, George R.; Barkoczy, Jozsef
PA Arizona Board of Regents, USA
SO Eur. Pat. Appl., 14 pp.
CODEN: EPXXDW
DT Patent
LA English
IC ICM C07K005-10
ICS A61K037-02
CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	EP 600745	A1	19940608	EP 1993-309708	19931203	<--
	EP 600745	B1	19970319			
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE					
	US 6034065	A	20000307	US 1992-985831	19921203	<--
	JP 07002894	A2	19950106	JP 1993-341075	19931201	<--
	JP 3451493	B2	20030929			
	CA 2110556	AA	19940604	CA 1993-2110556	19931202	<--
	CA 2110556	C	20030128			
	AT 150467	E	19970415	AT 1993-309708	19931203	<--
	ES 2101962	T3	19970716	ES 1993-309708	19931203	<--
PRAI	US 1992-985831	A	19921203	<--		

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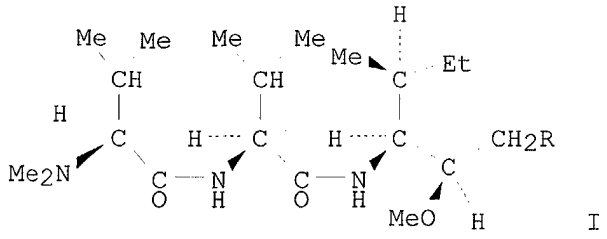

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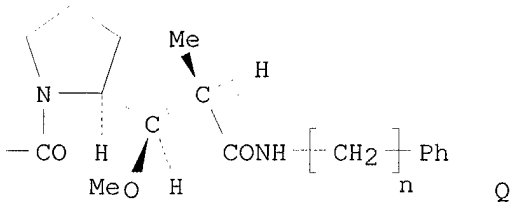
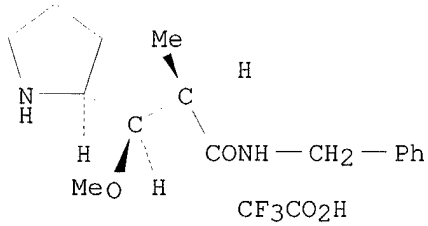


Q



II

AB The title compds. [I; R = Q; n = 1,2,3] having antineoplastic activity against leukemia, lung cancer, colon cancer, CNS cancer, melanoma cancer, and ovarian cancer cells (effective especially against Ovarian OVCAR-3; Central Nervous System ("CNS") SF295; Renal A498; Lung NCI460; Colon KM20L2 and Melanoma SK-MEL-3), were prepared E.g., I [R = CO2H] was condensed with the N-benzylpyrrolidinecarboxamide II (also prepared) to give I [R = Q, n = 1], which had an ED50 of <0.0001 mg/mL against ovarian OVCAR-3 cells.

ST antineoplastic tetrapeptide phenethylamide prepn; dolastatin analog prepn antineoplastic

IT **Neoplasm inhibitors**
(central nervous system, tetrapeptide phenethylamides analogs of dolastatin 10 as)

IT Nervous system
(central, neoplasm, inhibitors, tetrapeptide phenethylamides analogs of dolastatin 10 as)

IT **Neoplasm inhibitors**
(colon, tetrapeptide phenethylamides analogs of dolastatin 10 as)

IT Intestine, neoplasm
(colon, inhibitors, tetrapeptide phenethylamides analogs of dolastatin 10 as)

IT Lung, neoplasm
Ovary, neoplasm
(inhibitors, tetrapeptide phenethylamides analogs of dolastatin 10 as)

IT **Neoplasm inhibitors**
(leukemia, tetrapeptide phenethylamides analogs of dolastatin 10 as)

IT **Neoplasm inhibitors**
(lung, tetrapeptide phenethylamides analogs of dolastatin 10 as)

IT **Neoplasm inhibitors**
(melanoma, tetrapeptide phenethylamides analogs of dolastatin 10 as)

IT **Neoplasm inhibitors**
(ovary, tetrapeptide phenethylamides analogs of dolastatin 10 as)

IT Peptides, preparation
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(tetra-, phenethylamides analogs of dolastatin 10, preparation of, as antitumors)

IT 110417-88-4DP, Dolastatin 10, tetrapeptide phenethylamides analogs
149606-27-9P 149606-29-1P 149632-85-9P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as antitumor)

IT 149606-89-3P 149606-91-7P 149606-92-8P 159525-38-9P 159525-40-3P
159525-42-5P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as intermediate for antitumors)

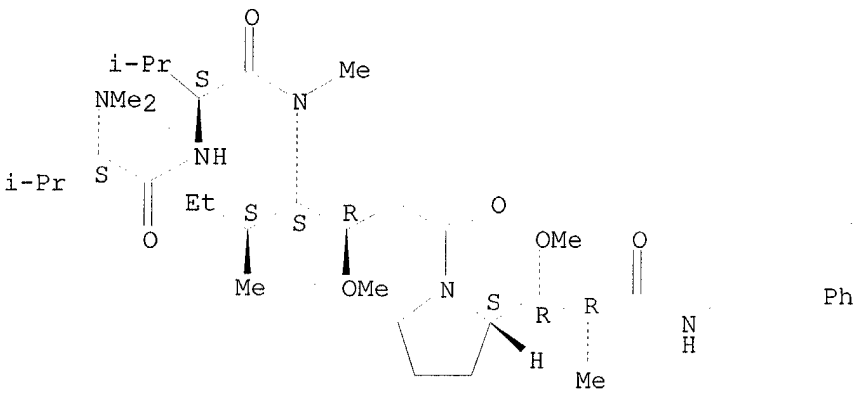
IT 64-04-0, Benzeneethanamine 100-46-9, Benzenemethanamine 2038-57-5, Benzenepropanamine 120205-50-7 133120-90-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, in preparation of antitumors)

IT **149606-27-9P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as antitumor)

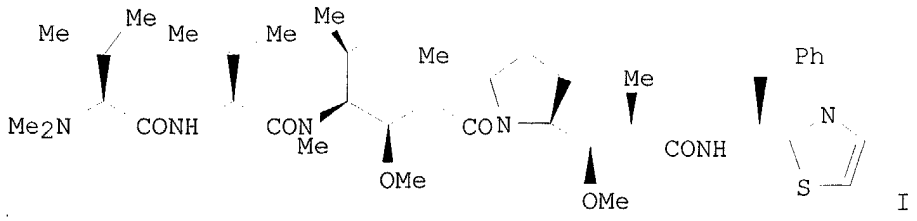
RN 149606-27-9 HCAPLUS

CN L-Valinamide, N,N-dimethyl-L-valyl-N-[(1S,2R)-2-methoxy-4-[(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-[(2-phenylethyl)amino]propyl]-1-pyrrolidinyl]-1-[(1S)-1-methylpropyl]-4-oxobutyl]-N-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L30 ANSWER 19 OF 20 HCAPLUS COPYRIGHT 2003 ACS on STN
AN 1995:16006 HCAPLUS
DN 122:10533
ED Entered STN: 08 Nov 1994
TI Synthesis of dolastatin 10 analogs
AU Miyazaki, Koichi; Gondo, Masaaki; Sakakibara, Kyoichi
CS Organ. Chem. Res. Dep., **Teikoku** Hormone Mfg.Co.,Ltd., Kawasaki, 213, Japan
SO Peptide Chemistry (**1993**), 31st, 85-8
CODEN: PECHDP; ISSN: 0388-3698
DT Journal
LA English
CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1
GI



AB A symposium report on the synthesis of 31 analogs of dolastatin 10 (I) and the anal. of their antineoplastic activities.

ST dolastatin 10 analog prepn antineoplastic symposium

IT **Neoplasm inhibitors**
(dolastatin 10 analogs)

IT Peptides, preparation
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(dolastatin 10-related, preparation and antineoplastic activity of)

IT Molecular structure-biological activity relationship
(neoplasm-inhibiting, of dolastatin 10 analogs)

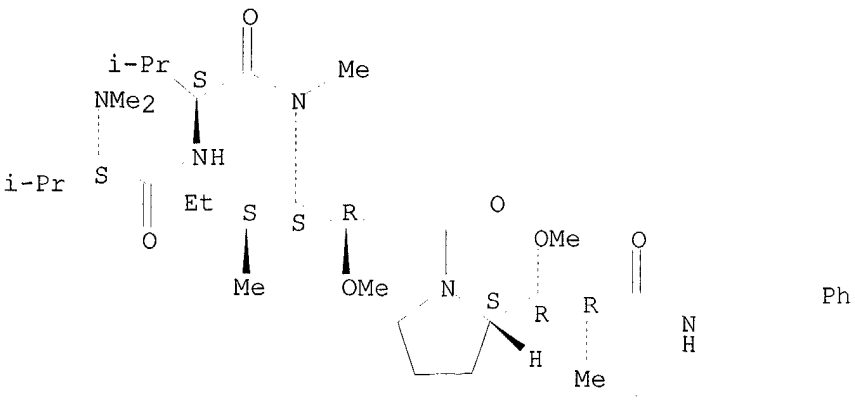
IT 110417-88-4DP, Dolastatin 10, analogs 149606-04-2P 149606-05-3P
149606-07-5P 149606-08-6P 149606-12-2P 149606-15-5P 149606-16-6P
149606-17-7P 149606-25-7P **149606-27-9P** 149606-28-0P
149606-29-1P 149606-31-5P 149606-34-8P 149632-86-0P 159255-63-7P
159255-64-8P 159255-65-9P 159255-66-0P 159255-67-1P 159255-68-2P
159255-69-3P 159255-70-6P 159255-71-7P 159255-72-8P 159255-73-9P
159255-74-0P 159255-75-1P 159255-76-2P 159255-77-3P 159255-78-4P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation and antineoplastic activity of)

IT **149606-27-9P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation and antineoplastic activity of)

RN 149606-27-9 HCAPLUS

CN L-Valinamide, N,N-dimethyl-L-valyl-N-[(1S,2R)-2-methoxy-4-[(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-[(2-phenylethyl)amino]propyl]-1-pyrrolidinyl]-1-[(1S)-1-methylpropyl]-4-oxobutyl]-N-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L30 ANSWER 20 OF 20 HCAPLUS COPYRIGHT 2003 ACS on STN
AN 1994:271185 HCAPLUS
DN 120:271185
ED Entered STN: 28 May 1994
TI Preparation of tetrapeptide derivatives as antitumor agents
IN Sakakibara, Kyoichi; Gondo, Masaaki; Miyazaki, Koichi
PA **Teikoku Hormone Mfg. Co., Ltd., Japan**
SO PCT Int. Appl., 84 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
IC ICM C07K005-06
ICS A61K037-02
CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	WO 9303054	A1	19930218	WO 1992-JP1005	19920806	<--
	W: AU, CA, JP, KR, US					
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE					
	AU 9224152	A1	19930302	AU 1992-24152	19920806	<--
	AU 662551	B2	19950907			
	EP 598129	A1	19940525	EP 1992-916961	19920806	<--
	EP 598129	B1	20000322			
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, SE					
	EP 934950	A1	19990811	EP 1998-115259	19920806	<--
	EP 934950	B1	20020410			
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, IE					
	AT 190983	E	20000415	AT 1992-916961	19920806	<--
	ES 2144421	T3	20000616	ES 1992-916961	19920806	<--
	SG 87056	A1	20020319	SG 1999-5131	19920806	<--
	AT 215962	E	20020415	AT 1998-115259	19920806	<--
	ES 2172069	T3	20020916	ES 1998-115259	19920806	<--
	US 6004934	A	19991221	US 1994-190194	19940209	<--
	AU 9520010	A1	19950720	AU 1995-20010	19950512	<--
	AU 673487	B2	19961107			
	US 5654399	A	19970805	US 1995-498688	19950703	<--
PRAI	JP 1991-223534	A	19910809	<--		
	JP 1991-225391	A	19910812	<--		
	EP 1992-916961	A3	19920806	<--		
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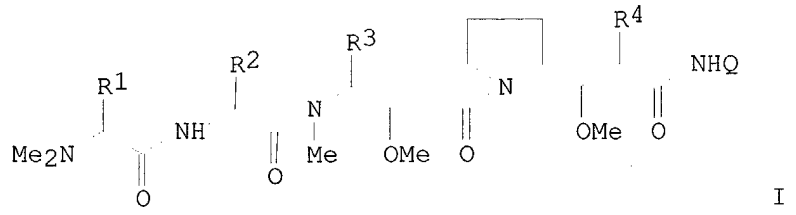
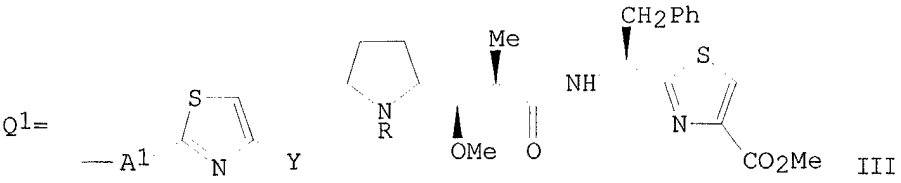
	US 1994-190194	A3	19940209	<--		

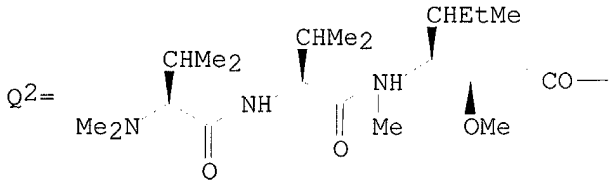
OS MARPAT 120:271185
GI



I



III



AB The title compds. (I; R1 - R4 = H, alkyl, aralkyl; Q = Q1, A2R7; A1 = direct bond, CHR5; R5 = H, alkyl, aralkyl; Y = COR6; R6 = HO, alkoxy, aralkyloxy, NR8R9; R8, R9 = H, alkyl, Ph, 4- to 7-membered ring heterocyclyl containing 1 or 2 heteroatoms selected from S, O, or N; or NR8R9 = 4- to 7-membered ring heterocyclyl containing one heteroatom selected from S, O, or N; R7 = cycloalkyl, aryl, indolyl; A2 = direct bond, alkylene), having a higher cytostatic activity than dolastatin 10, are prepared Thus, deprotection of a tripeptide (Q2-OCMe3)(preparation given) with concentrated HCl followed by treatment with Et3N in DMF gave a tripeptide carboxylic acid Q2-OH (II). Deprotection of an amide (III; R = CO2CMe3)(preparation given) with HCl in EtOAc followed by coupling with II in the presence of (EtO)2P(O)CN and Et3N in DMF gave 62% III (R = Q2) which showed ED50 of 2.4 + 10-7 μg/mL against P388 leukemia cells vs. 7.0 + 10-4 for dolastatin 10. A total of 39 I were prepared

ST tetrapeptide prepn antitumor

IT **Neoplasm inhibitors**
(tetrapeptide amides)

IT Peptides, preparation
RL: SPN (Synthetic preparation); PREP (Preparation)
(tetra-, preparation of, as antitumor agents)

IT 149606-04-2P 149606-05-3P 149606-06-4P 149606-07-5P 149606-08-6P
149606-09-7P 149606-10-0P 149606-11-1P 149606-12-2P 149606-13-3P
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149632-84-8P 149632-85-9P 149632-86-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of, as antitumor agent)

IT 118234-91-6P 119960-01-9P 120021-35-4P 120205-50-7P 120205-52-9P
120205-53-0P 120205-58-5P 132402-81-4P 147778-59-4P 149606-37-1P
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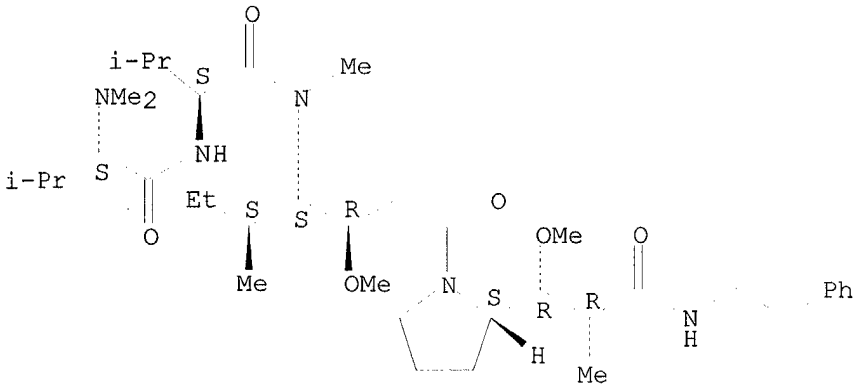
149606-94-0P 149606-95-1P 149606-96-2P 149606-98-4P 149632-87-1P
149632-88-2P 149632-89-3P 149664-79-9P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as intermediate for tetrapeptide antitumor agent)

IT 64-04-0, Phenethylamine 74-88-4, Methyl iodide, reactions 96-50-4, 2-Aminothiazole 100-51-6, Benzyl alcohol, reactions 115-11-7, Isobutene, reactions 140-11-4, Benzyl acetate 156-57-0 334-88-3, Diazomethane 1142-20-7 7664-41-7, Ammonia, reactions 38330-80-2 69610-41-9, N-tert-Butoxycarbonyl-L-prolinal 79069-50-4, N-tert-Butoxycarbonyl-L-alaninal 132402-74-5 133120-91-9 149606-97-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, in preparation of tetrapeptide antitumor agent)

IT **149606-27-9P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of, as antitumor agent)

RN 149606-27-9 HCAPLUS
CN L-Valinamide, N,N-dimethyl-L-valyl-N-[(1S,2R)-2-methoxy-4-[(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-[(2-phenylethyl)amino]propyl]-1-pyrrolidinyl]-1-[(1S)-1-methylpropyl]-4-oxobutyl]-N-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



=> => fil uspatall
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CA INDEXING COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'USPAT2' ENTERED AT 08:54:25 ON 11 DEC 2003
CA INDEXING COPYRIGHT (C) 2003 AMERICAN CHEMICAL SOCIETY (ACS)

=> d l34 bib abs kwic hitstr tot

L34 ANSWER 1 OF 4 USPATFULL on STN
AN 2003:87055 USPATFULL

TI Novel therapeutic agents for macromolecular structures
IN Griffin, John H., Atherton, CA, UNITED STATES
Christensen, Burton G., Alamo, CA, UNITED STATES
Jenkins, Thomas E., La Honda, CA, UNITED STATES
Judice, J. Kevin, El Granada, CA, UNITED STATES
PI US 2003060663 A1 20030327
AI US 2002-96270 A1 20020308 (10)
RLI Continuation of Ser. No. US 2000-510176, filed on 22 Feb 2000, PENDING
Continuation of Ser. No. US 1999-326660, filed on 7 Jun 1999, ABANDONED
PRAI US 1998-88464P 19980608 (60) <--
US 1998-92941P 19980715 (60) <--
DT Utility
FS APPLICATION
LREP ADVANCED MEDICINE, INC., 901 GATEWAY BOULEVARD, SOUTH SAN FRANCISCO, CA, 94080
CLMN Number of Claims: 61
ECL Exemplary Claim: 1
DRWN 41 Drawing Page(s)
LN.CNT 5057
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Disclosed are novel multibinding compounds (agents) which bind macromolecular structures including cellular, extracellular, and microbial components derived from vectors, viruses, fungi, yeasts, bacteria, and the like. The compounds of this invention comprise a plurality of ligands each of which can bind to such macromolecular structures thereby modulating the biological processes/functions thereof. Each of the ligands is covalently attached to a linker (framework) to provide for the multibinding compound. The linker is selected such that the multibinding compound so constructed demonstrates increased modulation or disruption of the biological processes/functions of cell as compared to the aggregate of the individual units of the ligand.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PRAI US 1998-88464P 19980608 (60) <--
PRAI US 1998-92941P 19980715 (60) <--
DETD . . . vinorelbine, vindesine,
Actin Lymphoma taxol, taxotere,
Testicular carcinoma colchicine, epothilone,
Fungal infection descodermolide,
Gout dolastatin 10,
Gouty arthritis anhydrovinblastine,
Neoplasm docetaxel, **TZT-1027**
,
desoxyepothilone B,
vinflunine, cemadotin,
dolastatin 15,
vinorelbine, CI-980, LY-355703, LY-355702,
cryptophycin, LY-290181, RPR-112378,
sarcodictyins, T-138067,
9-dihydrotaxanes, LL-15,. . .

L34 ANSWER 2 OF 4 USPATFULL on STN
AN 2001:63702 USPATFULL
TI Use of alkylated iminosugars to treat multidrug resistance
IN Jacob, Gary S., Creve Coeur, MI, United States
PA G.D. Searle & Company, Chicago, IL, United States (U.S. corporation)
PI US 6225325 B1 20010501
AI US 1998-189177 19981110 (9)
PRAI US 1997-65051P 19971110 (60) <--

DT Utility
FS Granted
EXNAM Primary Examiner: Jones, Dwayne C.
LREP Senniger, Powers, Leavitt & Roedel
CLMN Number of Claims: 42
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1991
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Methods and compositions for preventing, reducing, or reversing multidrug resistance (MDR) during cancer chemotherapy in patients undergoing treatment with therapeutically effective amounts of chemotherapeutic agents are provided. The methods comprise administering an anti-MDR effective amount of an N-substituted-1,5-dideoxy-1,5-imino-D-glucitol or galactitol iminosugar to a patient.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PRAI US 1997-65051P 19971110 (60) <--
SUMM **TZT-1027**

L34 ANSWER 3 OF 4 USPATFULL on STN
AN 1999:166975 USPATFULL
TI Tetrapeptide derivative
IN Sakakibara, Kyoichi, Tokyo, Japan
Gondo, Masaaki, Yokohama, Japan
Miyazaki, Koichi, Ebina, Japan
PA Teikoku Hormone Mfg. Co., Ltd., Tokyo, Japan (non-U.S. corporation)
PI US 6004934 19991221
WO 9303054 19930218 <--
AI US 1994-190194 19940209 (8)
WO 1992-JP1005 19920806
19940209 PCT 371 date
19940209 PCT 102(e) date
PRAI JP 1991-223534 19910809 <--
JP 1991-225391 19910812 <--
DT Utility
FS Granted
EXNAM Primary Examiner: Huff, Sheela
LREP Wenderoth, Lind & Ponack, L.L.P.
CLMN Number of Claims: 4
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1678
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A tetrapeptide derivative represented by the following formula or a salt thereof has a higher cytostatic activity than dolastatin 10, and is useful as an antitumor agent: ##STR1## wherein, R.sub.1, R.sub.2, R.sub.3 and R.sub.4 are the same or different and each represent a hydrogen atom, a lower alkyl group or an aralkyl group;

Q represents ##STR2## or a group of -A.sub.2 -R.sub.7, wherein, A.sub.1 represents a direct bond or ##STR3## Y represents a hydrogen atom or --COR.sub.6, R.sub.5 represents a hydrogen atom, a lower alkyl group or an aralkyl group,

R.sub.6 represents a hydroxyl group, a lower alkoxy group, an aralkyloxy group or ##STR4## wherein, R.sub.8 and R.sub.9 are the same or different and each represent a hydrogen atom, a lower alkyl group, a phenyl group or a 4- to 7-membered heterocyclic group containing one or two hetero atoms selected from S, O and N, or alternatively

R.sub.8 and R.sub.9 may combine together with the nitrogen atom to which they are bonded to form a 4- to 7-membered heterocyclic ring optionally

further containing one hetero atom selected from S, O and N,

A.sub.2 represents a direct bond or a lower alkylene group, and

R.sub.7 represents a cycloalkyl group, an aryl group or an indolyl group,

provided that the case is excluded where both R.sub.1 and R.sub.2 represent isopropyl groups, R.sub.3 represents a sec-butyl group, R.sub.4 represents a methyl group, and Q represents an α-(2-thiazolyl)phenethyl group.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

PI US 6004934 19991221
WO 9303054 19930218 <--
PRAI JP 1991-223534 19910809 <--
PRAI JP 1991-225391 19910812 <--

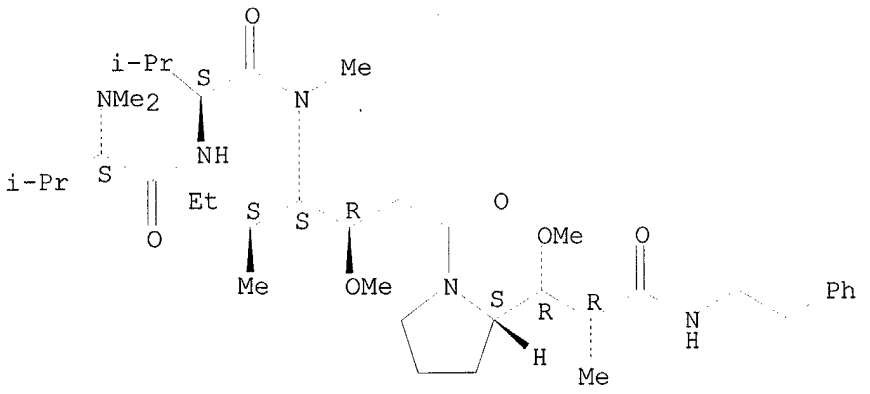
IT 149606-04-2P 149606-05-3P 149606-06-4P 149606-07-5P 149606-08-6P
149606-09-7P 149606-10-0P 149606-11-1P 149606-12-2P 149606-13-3P
149606-14-4P 149606-15-5P 149606-16-6P 149606-17-7P 149606-18-8P
149606-19-9P 149606-20-2P 149606-21-3P 149606-22-4P 149606-23-5P
149606-24-6P 149606-25-7P 149606-26-8P **149606-27-9P**
149606-28-0P 149606-29-1P 149606-30-4P 149606-31-5P 149606-32-6P
149606-33-7P 149606-34-8P 149606-35-9P 149606-36-0P 149632-83-7P
149632-84-8P 149632-85-9P 149632-86-0P
(preparation of, as antitumor agent)

IT **149606-27-9P**
(preparation of, as antitumor agent)

RN 149606-27-9 USPATFULL

CN L-Valinamide, N,N-dimethyl-L-valyl-N-[(1S,2R)-2-methoxy-4-[(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-[(2-phenylethyl)amino]propyl]-1-pyrrolidinyl]-1-[(1S)-1-methylpropyl]-4-oxobutyl]-N-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L34 ANSWER 4 OF 4 USPATFULL on STN

AN 97:68565 USPATFULL

TI Tetrapeptide derivative having antitumor activity

IN Sakakibara, Kyoichi, Tokyo, Japan
Gondo, Masaaki, Yokohama, Japan
Miyazaki, Koichi, Ebina, Japan

PA Teikoku Hormone Mfg. Co., Ltd., Tokyo, Japan (non-U.S. corporation)

PI US 5654399 19970805 <--

AI US 1995-498688 19950703 (8)

RLI Division of Ser. No. US 1994-190194, filed on 9 Feb 1994

PRAI JP 1991-223534 19910809 <--

JP 1991-225391 19910812 <--
DT Utility
FS Granted
EXNAM Primary Examiner: Scheiner, Toni R.; Assistant Examiner: Huff, Sheela J.
LREP Wenderoth, Lind & Ponack
CLMN Number of Claims: 4
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1774
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A tetrapeptide derivative represented by the following formula or a salt thereof has a higher cyto-static activity than dolastatin 10, and is useful as an antitumor agent: ##STR1## wherein, R.sub.1, R.sub.2, R.sub.3 and R.sub.4 are the same or different and each represent a hydrogen atom, a lower alkyl group or an aralkyl group;

Q represents ##STR2## or a group of --A.sub.2 --R.sub.7, wherein,

A.sub.1 represents a direct bond or ##STR3## Y represents a hydrogen atom or --COR.sub.6, R.sub.5 represents a hydrogen atom, a lower alkyl group or an aralkyl group,

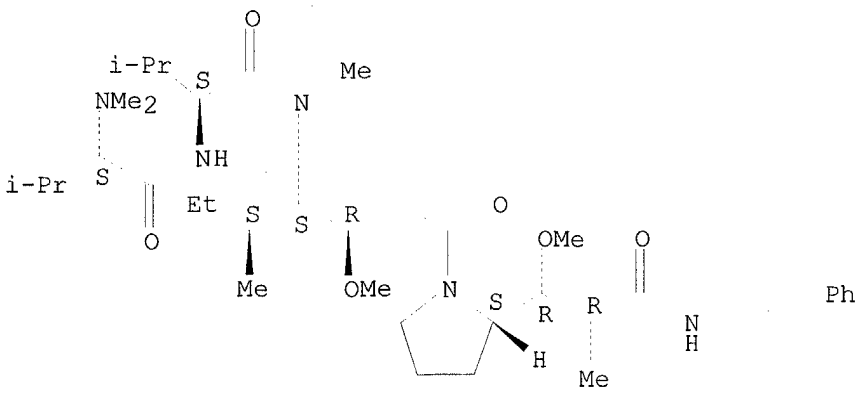
R.sub.6 represents a hydroxyl group, a lower alkoxy group, an aralkyloxy group or ##STR4## wherein, R.sub.8 and R.sub.9 are the same or different and each represent a hydrogen atom, a lower alkyl group, a phenyl group or a 4- to 7-membered heterocyclic group containing one or two hetero atoms selected from S, O and N, or alternatively R.sub.8 and R.sub.9 may combine together with the nitrogen atom to which they are bonded to form a 4- to 7-membered heterocyclic ring optionally further containing one hetero atom selected from S, O and N,

A.sub.2 represents a direct bond or a lower alkylene group, and

R.sub.7 represents a cycloalkyl group, an aryl group or an indolyl group, provided that the case is excluded where both R.sub.1 and R.sub.2 represent isopropyl groups, R.sub.3 represents a sec-butyl group, R.sub.4 represents a methyl group, and Q represents an α-(2-thiazolyl)phenethyl group.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
PI US 5654399 19970805 <--
PRAI JP 1991-223534 19910809 <--
PRAI JP 1991-225391 19910812 <--
IT 149606-04-2P 149606-05-3P 149606-06-4P 149606-07-5P 149606-08-6P
149606-09-7P 149606-10-0P 149606-11-1P 149606-12-2P 149606-13-3P
149606-14-4P 149606-15-5P 149606-16-6P 149606-17-7P 149606-18-8P
149606-19-9P 149606-20-2P 149606-21-3P 149606-22-4P 149606-23-5P
149606-24-6P 149606-25-7P 149606-26-8P **149606-27-9P**
149606-28-0P 149606-29-1P 149606-30-4P 149606-31-5P 149606-32-6P
149606-33-7P 149606-34-8P 149606-35-9P 149606-36-0P 149632-83-7P
149632-84-8P 149632-85-9P 149632-86-0P
(preparation of, as antitumor agent)
IT **149606-27-9P**
(preparation of, as antitumor agent)
RN 149606-27-9 USPATFULL
CN L-Valinamide, N,N-dimethyl-L-valyl-N-[(1S,2R)-2-methoxy-4-[(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-[(2-phenylethyl)amino]propyl]-1-pyrrolidinyl]-1-[(1S)-1-methylpropyl]-4-oxobutyl]-N-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



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FILE COVERS 1974 TO 4 Dec 2003 (20031204/ED)

EMBASE has been reloaded. Enter HELP RLOAD for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d all tot

L36 ANSWER 1 OF 13 EMBASE
on STN
AN 2000019753 EMBASE
TI Modulation of cIAP-1 by novel antitubulin agents when combined with bryostatin 1 results in increased apoptosis in the human early pre-B acute lymphoblastic leukemia cell line Reh.
AU Wall N.R.; Mohammad R.M.; Nabha S.M.; Pettit G.R.; Al-Katib A.M.
CS N.R. Wall, Department of Internal Medicine, Karmanos Cancer Institute, Wayne State Univ. School Medicine, Detroit, MI 48201, United States
SO Biochemical and Biophysical Research Communications, (9 Dec 1999) 266/1 (76-80).
Refs: 35
ISSN: 0006-291X CODEN: BBRCA
CY United States
DT Journal; Article
FS 016 Cancer
025 Hematology
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB Previous studies have shown that bryostatin 1 induces a decrease in the expression of the antiapoptotic protooncogene Bcl-2 in the human acute lymphoblastic leukemia (ALL) cell line Reh. This down-regulation has been shown to reduce drug resistance of the Reh cells to anti-tubulin polymerization agents. In the present study we investigated the effect of bryostatin 1 alone and in combination with novel anti-tubulin agents (dolastatin 10 and **auristatin PE**) and the chemotherapeutic vincristine on the inhibitor of apoptosis protein cIAP-1. Cells were cultured with bryostatin 1 (1 nM), dolastatin 10 (0.1 ng/ml),

auristatin PE (0.1 ng/ml), or vincristine (0.5 ng/ml) alone or the combination of these anti-tubulins with bryostatin 1. Western blots were conducted to assess the effects of the above agents on cIAP-1 protein level. Flow-cytometric analysis [7-amino-actinomycin D (7AAD)] was conducted to assess apoptosis as well as staining for morphology using tetrachrome stain. Our results show that cIAP-1 is induced in a time-dependent fashion after bryostatin 1 exposure up to 72 h. However, upon treatment of cells with a combination of bryostatin 1 and dolastatin 10 or **auristatin PE**, the induction of cIAP-1 was abolished, leading to a significant increase in apoptosis. The initial 24- and 48-h reduction in cIAP-1 protein level recorded in the bryostatin 1 and vincristine combination recovered to control levels by 72 h. We believe that this phenomenon is responsible for the reduced apoptosis recorded in this combination. Results of this study should prove useful in guiding the clinical application of these novel agents in the treatment of ALL.

CT Medical Descriptors:
*apoptosis
*acute lymphoblastic leukemia
leukemia cell
proto oncogene
down regulation
drug resistance
polymerization
drug effect
cancer cell culture
immunoblotting
flow cytometry
cell structure
human
controlled study
human cell
article
priority journal
Drug Descriptors:
*bryostatin 1: CB, drug combination
*bryostatin 1: PD, pharmacology
*inhibitor of apoptosis protein: EC, endogenous compound
protein bcl 2: EC, endogenous compound
tubulin: EC, endogenous compound
dolastatin 10: CB, drug combination
dolastatin 10: PD, pharmacology
auristatin PE: CB, drug combination
auristatin PE: PD, pharmacology
vincristine: CB, drug combination
vincristine: PD, pharmacology

RN (bryostatin 1) 83314-01-6; (dolastatin 10) 110417-88-4; (**auristatin PE**) **149606-27-9**; (vincristine) 57-22-7

L36 ANSWER 2 OF 13 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 1999401758 EMBASE
TI Activity of a novel antitumor agent, **TZT-1027**.
AU Kobayashi M.; Natsume T.; Watanabe J.-I.; Fujio N.; Mikami T.; Miyasaka K.; Tsukagoshi S.
CS M. Kobayashi, Pharmacological Research Department, Teikoku Hormone Mfg. Co., Ltd., 1604 Shimo-sakunobe, Takatsu-ku, Kawasaki 213-8522, Japan
SO Folia Pharmacologica Japonica, (1999) 114/SUPPL. 1 (230P-235P).
Refs: 7
ISSN: 0015-5691 CODEN: NYKZAU
CY Japan
DT Journal; Article

FS 016 Cancer
030 Pharmacology
037 Drug Literature Index
LA Japanese
SL English; Japanese
AB We studied the antitumor activity of newly synthesized dolastatin 10 analogs. **TZT-1027** showed remarkable activity and was selected for further development. **TZT-1027** was found to inhibit the assembly of porcine brain microtubule proteins and to depolymerize the polymerized microtubule proteins. Therefore, its mechanism of antitumor activity seems to be at least partially ascribed to the inhibition of microtubule assembly. We further studied the binding site of **TZT-1027** on tubulin. Scatchard analysis of 3H-**TZT-1027** binding data suggested two binding sites including a high affinity site and a low affinity site. **TZT-1027** affected the binding of vinblastine (VBL) on tubulin but its binding site isn't identical to the VBL binding site. **TZT-1027** induced apoptosis within 24 h, not only in human leukemia cells such as HL-60, but also in solid tumors such as human prostate carcinoma cells DU145 and human mammary carcinoma cells MCF-7. **TZT-1027** showed good antitumor activity against human xenografts (MX-1 and LX-1) without causing serious body weight reduction, which resulted in tumor regression. We examined the effect of **TZT-1027** on the established tumor vasculature using the dye perfusion into tumor. **TZT-1027** exhibited considerable antivascular activity in tumor sections in addition to excellent cytotoxic effect.
CT Medical Descriptors:
*antineoplastic activity
*microtubule assembly
depolymerization
drug mechanism
drug binding site
scatchard plot
apoptosis
leukemia cell
prostate carcinoma
breast carcinoma
tumor xenograft
cell strain hl 60
cell strain mcf 7
weight reduction
tumor regression
tumor vascularization
drug cytotoxicity
human
nonhuman
mouse
animal experiment
animal model
controlled study
human cell
article
Drug Descriptors:
***tzt 1027: DV, drug development**
***tzt 1027: PD, pharmacology**
*antineoplastic agent: DV, drug development
*antineoplastic agent: PD, pharmacology
microtubule protein: EC, endogenous compound
tubulin
tritium
vinblastine
dolastatin

vincristine
colchicine
RN (tritium) 10028-17-8; (vinblastine) 865-21-4; (vincristine) 57-22-7; (colchicine) 64-86-8
CN **Tzt 1027**

L36 ANSWER 3 OF 13 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 1999371857 EMBASE
TI Clonal preservation of human pancreatic cell line derived from primary pancreatic adenocarcinoma.
AU Mohammad R.M.; Li Y.; Mohamed A.N.; Pettit G.R.; Adsay V.; Vaitkevicius V.K.; Al-Katib A.M.; Sarkar F.H.
CS Dr. F.H. Sarkar, Department of Pathology, Wayne State Univ. School of Medicine, 9374 Scott Hall, 540 E. Canfield Avenue, Detroit, MI 48201, United States. fsarkar@med.wayne.edu
SO Pancreas, (1999) 19/4 (353-361).
Refs: 18
ISSN: 0885-3177 CODEN: PANCE4
CY United States
DT Journal; Article
FS 016 Cancer
037 Drug Literature Index
048 Gastroenterology
LA English
SL English
AB Adenocarcinoma of the pancreas generally remains an incurable disease by available treatment modalities, demanding the development of a suitable cell- culture/animal model and the discovery and evaluation of novel therapeutic agents. We report the clonal preservation of a human pancreatic cell line (KCI-MOH1) established from a 74-year-old African-American man diagnosed with pancreatic cancer. Initially the human primary tumor was grown as a xenograft in SCID mice and, subsequently, a cell line was established from tumors grown as a xenograft as reported in our earlier publication. The molecular characterization of the primary tumor, the tumors grown as xenograft, and the cell line all revealed similar genotypic properties. By using an automated DNA sequencer, a K-ras mutation (codon 12, GGT to CGT, Gly to Arg) was detected in the pancreatic tumor tissue taken from the patient, whereas no p53 mutation was detected. The same K-ras mutation and unaltered p53 was also found in the xenograft tumor and in the KCI-MOH1 cell line. Chromosome analysis of the cultured cells revealed: 42,XY,add(3)(p11.2),der(7)t(7;12) (p22;q12),-10,-12,add (14)(p11),-18,add (20)(q13),-22/84, idemx2, which is the same chromosome complement found in xenograft tumors. The KCI-MOH1 cell line grows well in tissue culture and forms tumors in the SCID mice when implanted subcutaneously, as well as in orthotopic sites. The KCI-MOH1 cell line-derived SCID mouse xenograft model was used for efficacy evaluation of bryostatin 1, **auristatin-PE**, spongistatin 1, and gemcitabine alone and in combination. Tumor growth inhibition (T/C expressed as percentage), tumor growth delay (T - C), and log 10 kill for these agents were 38%, 22 days, and 0.53; 15%, 30 days, and 0.80; 24%, 25 days, and 0.66; and 10%, 33 days, and 0.90, respectively. When given in combination, two of seven gemcitabine + **auristatin-PE** -treated animals were free of tumors for 150 days and were considered cured. Animals treated with a combination of bryostatin 1 and gemcitabine and a combination of spongistatin and gemcitabine produced remissions in only one of seven mice. From these results, we conclude that (a) this is the first study illustrating that clonal characteristics of primary pancreatic tumors remained unchanged when implanted in mice and as a permanent cell line grown in vitro; and (b) there is a synergistic effect between gemcitabine and selected marine products tested in this study, which is more apparent in the gemcitabine and **auristatin-PE** combination. The results of this preliminary study suggest that

these agents should be explored clinically in the treatment of pancreatic cancer.

CT Medical Descriptors:
*pancreas adenocarcinoma: DT, drug therapy
*pancreas cell
*cancer cell culture
*preservation
tumor xenograft
oncogene k ras
gene mutation
chromosome analysis
cancer growth
cancer regression
cancer inhibition
drug efficacy
antineoplastic activity
human
nonhuman
male
female
mouse
animal experiment
animal model
controlled study
human cell
animal tissue
aged
article
priority journal
Drug Descriptors:
*bryostatin 1: CB, drug combination
*bryostatin 1: CM, drug comparison
*bryostatin 1: DT, drug therapy
*gemcitabine: CB, drug combination
*gemcitabine: CM, drug comparison
*gemcitabine: DT, drug therapy
*antineoplastic agent: CB, drug combination
*antineoplastic agent: CM, drug comparison
*antineoplastic agent: DT, drug therapy
*spongistatin 1: CB, drug combination
*spongistatin 1: CM, drug comparison
*spongistatin 1: DT, drug therapy
***auristatin pe: CB, drug combination**
***auristatin pe: CM, drug comparison**
***auristatin pe: DT, drug therapy**
RN (bryostatin 1) 83314-01-6; (gemcitabine) 103882-84-4

L36 ANSWER 4 OF 13 EMBASE
on STN
AN 1999342310 EMBASE
TI Bax:Bcl-2 ratio modulation by bryostatin 1 and novel antitubulin agents is important for susceptibility to drug induced apoptosis in the human early pre-B acute lymphoblastic leukemia cell line, Reh.
AU Wall N.R.; Mohammad R.M.; Al-Katib A.M.
CS A.M. Al-Katib, Department of Internal Medicine, Karmanos Cancer Institute, Wayne State Univ. School of Medicine, PO Box 02143, Detroit, MI 48201, United States. alkatib@karmanos.org
SO Leukemia Research, (1999) 23/10 (881-888).
Refs: 52
ISSN: 0145-2126 CODEN: LEREDD
PUI S 0145-2126(99)00108-3
CY United Kingdom
DT Journal; Article

FS 005 General Pathology and Pathological Anatomy
016 Cancer
025 Hematology
LA English
SL English
AB The ratio of Bax to Bcl-2 protein can determine whether cells will die via apoptosis or be protected from it. Reh was found to express a high basal level of Bcl-2 but was lacking of Bax protein expression. Treatment with bryostatin 1 induced a down-regulation in Bcl-2 protein that was not accompanied by an obvious Bax protein induction or apoptosis. These results suggest that a decreased level of Bcl-2 alone in this cell line is not sufficient for apoptosis induction. In an effort to identify the mechanism whereby apoptosis could be induced in this ALL model, we treated Reh cells with three microtubule inhibitors: dolastatin 10, **auristatin PE** and vincristine, in the presence and absence of bryostatin 1. When used alone, only dolastatin 10 induced apoptosis that was detected morphologically, and by flow cytometry. Western blots revealed that dolastatin 10-induced apoptosis was accompanied by the induction of Bax protein and the reduction in Bcl-2 protein. **Auristatin PE** and vincristine induced both Bax and Bcl-2 protein, leaving the Bax:Bcl-2 ratio constant. Reh cells pretreated for 24 h with bryostatin 1 followed by dolastatin 10, **auristatin PE** or vincristine showed significant apoptosis which was accompanied by Bcl-2 protein down regulation and Bax protein up regulation. We conclude that: (1) expression of bax is necessary for apoptosis-induction in this model; (2) a decrease in Bcl-2 level alone is not sufficient and might not be necessary for apoptosis-induction; and (3) the ratio of Bax:Bcl-2 plays a critical role in susceptibility to apoptosis in Reh cells. The results from this study should prove useful in guiding the clinical application of these novel agents in the treatment of acute lymphoblastic leukemia.
CT Medical Descriptors:
*apoptosis
*acute lymphoblastic leukemia: ET, etiology
protein expression
signal transduction
cancer inhibition
cell death
human
controlled study
human cell
article
priority journal
Drug Descriptors:
*protein bax: EC, endogenous compound
*protein bcl 2: EC, endogenous compound
*bryostatin 1: EC, endogenous compound
RN (bryostatin 1) 83314-01-6

L36 ANSWER 5 OF 13 EMBASE
on STN
AN 1999202172 EMBASE
TI **TZT-1027.** Antineoplastic.
AU Hoshi A.; Leeson P.; Castaner J.
CS A. Hoshi, 3-4-10 Kameari, Katsushika-ku, Tokyo 125-0061, Japan
SO Drugs of the Future, (1999) 24/4 (404-409).
Refs: 34
ISSN: 0377-8282 CODEN: DRFUD4
CY Spain
DT Journal; General Review
FS 016 Cancer
029 Clinical Biochemistry
030 Pharmacology

037 Drug Literature Index
LA English
CT Medical Descriptors:
*antineoplastic activity
drug synthesis
drug structure
drug potentiation
human
nonhuman
intravenous drug administration
intraperitoneal drug administration
review
Drug Descriptors:
***auristatin phenethylamide: AD, drug administration**
***auristatin phenethylamide: AN, drug analysis**
***auristatin phenethylamide: CB, drug combination**
***auristatin phenethylamide: CM, drug comparison**
***auristatin phenethylamide: DV, drug development**
***auristatin phenethylamide: IT, drug interaction**
***auristatin phenethylamide: PD, pharmacology**
*antineoplastic agent: AD, drug administration
*antineoplastic agent: AN, drug analysis
*antineoplastic agent: CB, drug combination
*antineoplastic agent: CM, drug comparison
*antineoplastic agent: DV, drug development
*antineoplastic agent: IT, drug interaction
*antineoplastic agent: PD, pharmacology
dolastatin 10: CB, drug combination
dolastatin 10: CM, drug comparison
cisplatin: CM, drug comparison
fluorouracil: CM, drug comparison
vincristine
doxorubicin
bryostatin 1: CB, drug combination
bryostatin 1: CM, drug comparison
gemcitabine: CB, drug combination
gemcitabine: CM, drug comparison
tubulin: EC, endogenous compound
cytarabine: IT, drug interaction
tzt 1027
RN (dolastatin 10) 110417-88-4; (cisplatin) 15663-27-1, 26035-31-4, 96081-74-2; (fluorouracil) 51-21-8; (vincristine) 57-22-7; (doxorubicin) 23214-92-8, 25316-40-9; (bryostatin 1) 83314-01-6; (gemcitabine) 103882-84-4; (cytarabine) 147-94-4, 69-74-9
CN **(1) Tzt 1027**
CO (1) Teikoku Hormone (Japan)

L36 ANSWER 6 OF 13 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 1998156024 EMBASE
TI Successful treatment of human chronic lymphocytic leukemia xenografts with combination biological agents **auristatin PE** and bryostatin 1.
AU Mohammad R.M.; Varterasian M.L.; Almatchy V.P.; Hannoudi G.N.; Pettit G.R.; Al-Katib A.
CS R.M. Mohammad, Division of Hematology and Oncology, Wayne State Univ. School of Medicine, P.O. Box 02143, Detroit, MI 48201, United States. Mohammad@oncgate.roc.wayne.edu
SO Clinical Cancer Research, (1998) 4/5 (1337-1343).
Refs: 24
ISSN: 1078-0432 CODEN: CCREF4
CY United States
DT Journal; Article

FS 016 Cancer
025 Hematology
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB We tested the activity of dolastatin 10 (a natural product derived from the shell-less marine mollusk, Dolabella auricularia, a sea hare) and its structural modification, **auristatin PE**, alone and in combination with bryostatin 1 (a protein kinase C activator derived from the marine bryozoan Bugula neritina) on a human B-cell chronic lymphocytic leukemia cell line (WSU-CLL) and in a severe combined immune deficient (SCID) mouse xenograft model bearing this cell line. WSU-CLL cells were cultured in RPMI 1640 at a concentration of 2 x 105/ml using a 24-well plate. Agents were added to triplicate wells, and cell count, viability, mitosis, and apoptosis were assessed after 24 h of incubation at 37°C. Results showed that dolastatin 10 had no apparent inhibition of cell growth at concentrations less than 500 pg/ml. **Auristatin PE**, on the other hand, showed significant growth inhibition at concentrations as low as 50 pg/ml. **Auristatin PE** -treated cultures, at this concentration, exhibited 27 and 4.5% mitosis and apoptosis, respectively. Dolastatin 10, at the same concentration, did not exert any effect and was comparable with that of control cultures. In the WSU-CLL-SCID mouse xenograft model, the efficacy of these agents alone and in combination with bryostatin 1 was evaluated. Tumor growth inhibition (T/C), tumor growth delay (T-C), and log10 kill for dolastatin 10, **auristatin PE**, and bryostatin 1 were 14%, 25 days, and 1.98; 2%, 25 days, and 1.98; 19%, 13 days, and 1.03, respectively. **Auristatin-PE** produced cure in three of five mice, whereas dolastatin 10 showed activity but no cures. When given in combination, **auristatin PE** + bryostatin 1-treated animals were all free of tumors (five of five) for 150 days and were considered cured. Dolastatin 10 + bryostatin 1-treated animals produced cure in only two of five mice. We conclude that: (a) **auristatin-PE** is more effective in this model than dolastatin 10; (b) **auristatin PE** can be administered at a concentration 10 times greater than dolastatin 10; (c) there is a synergetic effect between these agents and bryostatin 1, which is more apparent in the bryostatin 1 + **auristatin PE** combination. The use of these agents should be explored clinically in the treatment of CLL.
CT Medical Descriptors:
*chronic lymphatic leukemia: DT, drug therapy
*cancer chemotherapy
b cell leukemia: DT, drug therapy
nude mouse
xenograft
cancer growth
growth inhibition
drug potentiation
drug isolation
mollusc
human
nonhuman
female
mouse
animal model
controlled study
human cell
intravenous drug administration
intraperitoneal drug administration
article
priority journal
Drug Descriptors:

*dolastatin 10: AD, drug administration
*dolastatin 10: CB, drug combination
*dolastatin 10: CM, drug comparison
*dolastatin 10: DO, drug dose
*dolastatin 10: IT, drug interaction
*dolastatin 10: DT, drug therapy
***auristatin pe: AD, drug administration**
***auristatin pe: CB, drug combination**
***auristatin pe: CM, drug comparison**
***auristatin pe: DO, drug dose**
***auristatin pe: IT, drug interaction**
***auristatin pe: DT, drug therapy**
*bryostatin 1: AD, drug administration
*bryostatin 1: CB, drug combination
*bryostatin 1: CM, drug comparison
*bryostatin 1: DO, drug dose
*bryostatin 1: IT, drug interaction
*bryostatin 1: DT, drug therapy
antineoplastic agent: AD, drug administration
antineoplastic agent: CB, drug combination
antineoplastic agent: CM, drug comparison
antineoplastic agent: DO, drug dose
antineoplastic agent: IT, drug interaction
antineoplastic agent: DT, drug therapy
natural product: AD, drug administration
natural product: CB, drug combination
natural product: CM, drug comparison
natural product: DO, drug dose
natural product: IT, drug interaction
natural product: DT, drug therapy
unclassified drug
RN (dolastatin 10) 110417-88-4; (bryostatin 1) 83314-01-6

L36 ANSWER 7 OF 13 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 1998134322 EMBASE
TI An orthotopic model of human pancreatic cancer in severe combined immunodeficient mice: Potential application for preclinical studies.
AU Mohammad R.M.; Ai-Katib A.; Pettit G.R.; Vaitkevicius V.K.; Joshi U.; Adsay V.; Majumdar A.P.N.; Sarkar F.H.
CS F.H. Sarkar, Department of Pathology, Wayne State Univ. School of Medicine, 9374 Scott Hall, 540 East Canfield Avenue, Detroit, MI 48201, United States. fsarkar@med.wayne.edu.
SO Clinical Cancer Research, (1998) 4/4 (887-894).
Refs: 25
ISSN: 1078-0432 CODEN: CCREF4
CY United States
DT Journal; Article
FS 016 Cancer
037 Drug Literature Index
LA English
SL English
AB Pancreatic adenocarcinoma is one of the most incurable and least understood of all human cancers. It is the fourth leading cause of cancer-related mortality in males (after lung, prostate, and colon) and in females (after lung, breast, and colon) in the United States with <2-3% of patients surviving >5 years. In an attempt to search for more effective therapies for this disease, we report here, for the first time, an effective treatment, the combination of gemcitabine and **auristatin** -phenethylamine (PE), against an orthotopic implantation of a human pancreatic adenocarcinoma cell line (HPAC) in severe combined immunodeficient (SCID) mice. Tumor implantation was performed by injecting 100 μl of the HPAC cell suspension (1 x 106 cells) directly into the

pancreas of 5-week-old SCID mice. After implantation, tumor formation was checked twice a week. All palpable tumors were detected within 21 days (100% take rate), and tumors were confirmed histologically to be pancreatic adenocarcinoma. For the subsequent efficacy trial, tumor-bearing SCID mice were randomized into four groups with five mice in each group. One served as a control, the second received gemcitabine alone (2.5 mg/kg/injection i.p.), the third received **auristatin-PE** alone (2.0 mg/kg/injection i.v.), and the fourth group received the combination of gemcitabine (i.p.) and **auristatin-PE** (1.5 mg/kg/injection i.v.). All animals were euthanized 7 days after the completion of their treatments, and the pancreases were resected. Histological examination revealed the tumors to be adenocarcinoma. The tumors were composed of diffuse sheets of cells interrupted by glandular spaces containing secretory material. Cytologically, the tumor cells were large, pleomorphic, and hyperchromatic. Many cells contained intracellular lumina containing mucin. Immunohistochemical studies showed strong p21(WAFI) (p21) expression but no immunoreactivity with p53 and Her-2/neu antibodies. The mean pancreatic weight in the gemcitabine/**auristatin-PE** combination group was significantly ($P = 0.014$) lower (0.84 ± 0.639 g) when compared with those of the control (2.91 ± 1.19 g) and gemcitabine alone (1.84 ± 0.796 g; $P = 0.064$) groups. In addition, the mean weight in the combination group approached statistical significance when compared with the **auristatin-PE** group alone (1.16 ± 0.635 g; $P = 0.028$). We conclude that the combination of gemcitabine and **auristatin-PE** is an effective treatment against HPAC tumors in this xenograft model and more effective than treatment with either gemcitabine or **auristatin-PE** alone and could be considered for future animal studies with pancreas cancer and/or for human clinical trials.

CT Medical Descriptors:
*pancreas cancer: DT, drug therapy
*scid mouse
pancreas adenocarcinoma
cancer transplantation
immunohistochemistry
antineoplastic activity
human
nonhuman
female
animal experiment
animal model
controlled study
human cell
article
priority journal
Drug Descriptors:
*gemcitabine: AN, drug analysis
*gemcitabine: CB, drug combination
*gemcitabine: DV, drug development
*gemcitabine: DO, drug dose
*gemcitabine: DT, drug therapy
***auristatin phenethylamine: AN, drug analysis**
***auristatin phenethylamine: CB, drug combination**
***auristatin phenethylamine: DV, drug development**
***auristatin phenethylamine: DO, drug dose**
***auristatin phenethylamine: DT, drug therapy**
*dolastatin 10: AN, drug analysis
*dolastatin 10: DV, drug development
protein p21
protein p53
unclassified drug

RN (gemcitabine) 103882-84-4; (dolastatin 10) 110417-88-4; (protein p21) 85306-28-1

L36 ANSWER 8 OF 13 EMBASE
on STN
AN 1998056305 EMBASE
TI Synergistic interaction of selected marine animal anticancer drugs against human diffuse large cell lymphoma.
AU Mohammad R.M.; Pettit G.R.; Almatchy V.P.; Wall N.; Varterasian M.; Al-Katib A.
CS R.M. Mohammad, Department of Internal Medicine, Wayne State University Sch Medicine, Karmanos Cancer Institute, Detroit, MI 48201, United States
SO Anti-Cancer Drugs, (1998) 9/2 (149-156).
Refs: 22
ISSN: 0959-4973 CODEN: ANTDEV
CY United Kingdom
DT Journal; Article
FS 016 Cancer
025 Hematology
037 Drug Literature Index
LA English
SL English
AB We studied the antitumor effects of dolastatin 10, its structural modification, **auristatin PE** (**TZT-1027**), and vincristine alone and in combination with bryostatin 1 on a human diffuse large cell lymphoma line (WSU-DLCL2) in vitro and in vivo WSU-DLCL2, cells were cultured in RPMI 1640 at a concentration of 2 x 105/ml using a 24-well plate. Agents were added to triplicate wells, and cell count, viability, mitosis and apoptosis were assessed. Dolastatin 10 showed no apparent inhibition of cell growth at concentrations less than 500 pg/ml. **Auristatin PE** showed significant growth inhibition at concentrations as low as 10 pg/ml, while vincristine had a minimal effect at 50 pg/ml. Dolastatin 10, **auristatin** RE and vincristine-treated cultures, at 50 pg/ml, exhibited 11, 1.7; 45, 11.8%; and 39, 25% mitosis and apoptosis, respectively. In the WSU-DLCL2 SCID mouse xenograft model, the efficacy of these agents alone or in combination with bryostatin 1 was evaluated. Tumor growth inhibition (T/C), tumor growth delay (T-C) and log10, kill for dolastatin 10, **auristatin PE**, vincristine and bryostatin 1 were 30%, 14 days and 1.4; 0.0%, 55 days and 5.5; 29.6%, 16 days and 1.6; and 39%, 7 days and 0.7, respectively. When given in combination, two out of five mice treated with **auristatin PE** + bryostatin 1 were free of tumors for 150 days and were considered cured. Dolastatin 10 + bryostatin 1 and vincristine + bryostatin 1 combinations were highly active but no cure was observed. We conclude that: (i) **auristatin** RE is more effective in this model than dolastatin 10, vincristine or bryostatin 1, (ii) **auristatin PE** can be administered at a concentration 10 times greater than dolastatin 10, and (iii) there is a synergistic effect between these agents and bryostatin 1, which is more apparent in the bryostatin 1 + **auristatin** RE combination. The use of these agents should be further explored clinically in the treatment of lymphoma.
CT Medical Descriptors:
*drug potentiation
*large cell lymphoma: TH, therapy
cancer cell culture
culture medium
cell count
cell viability
mitosis
apoptosis
cell growth
concentration response
xenograft
cancer inhibition

human
nonhuman
female
animal experiment
animal model
controlled study
human cell
article
priority journal
Drug Descriptors:
*antineoplastic agent: CB, drug combination
*antineoplastic agent: CM, drug comparison
*antineoplastic agent: CR, drug concentration
*antineoplastic agent: IT, drug interaction
*antineoplastic agent: PD, pharmacology
dolastatin 10: CB, drug combination
dolastatin 10: CM, drug comparison
dolastatin 10: CR, drug concentration
dolastatin 10: IT, drug interaction
dolastatin 10: PD, pharmacology
tzt 1027: CB, drug combination
tzt 1027: CM, drug comparison
tzt 1027: CR, drug concentration
tzt 1027: IT, drug interaction
tzt 1027: PD, pharmacology
auristatin pe: CB, drug combination
auristatin pe: CM, drug comparison
auristatin pe: CR, drug concentration
auristatin pe: IT, drug interaction
auristatin pe: PD, pharmacology
bryostatin 1: CB, drug combination
bryostatin 1: CM, drug comparison
bryostatin 1: IT, drug interaction
bryostatin 1: PD, pharmacology
vincristine: CB, drug combination
vincristine: CM, drug comparison
vincristine: IT, drug interaction
vincristine: PD, pharmacology
unclassified drug
RN (dolastatin 10) 110417-88-4; (bryostatin 1) 83314-01-6; (vincristine) 57-22-7
CN **Tzt 1027**
CO Sigma (United States)

L36 ANSWER 9 OF 13 EMBASE
on STN
AN 1998023272 EMBASE
TI Establishment of a human pancreatic tumor xenograft model: Potential application for preclinical evaluation of novel therapeutic agents.
AU Mohammad R.M.; Dugan M.C.; Mohamed A.N.; Almatchy V.P.; Flake T.M.; Dergham S.T.; Shields A.F.; Al-Katib A.A.; Vaitkevicius V.K.; Sarkar F.H.
CS Dr. F.H. Sarkar, Department of Pathology, Wayne State Univ. School of Medicine, 540 East Canfield Avenue, Detroit, MI 48201, United States
SO Pancreas, (1998) 16/1 (19-25).
Refs: 22
ISSN: 0885-3177 CODEN: PANCE4
CY United States
DT Journal; Conference Article
FS 016 Cancer
037 Drug Literature Index
048 Gastroenterology
LA English
SL English

AB Adenocarcinoma of the pancreas is currently the fifth leading cause of death in the United States. It remains generally incurable by available treatment modalities. We report here on the characterization of a permanent pancreatic cell line (KCI-MOH1), established as a xenograft in severe combined immune deficient (SCID) mice, from a 74 year-old African American male patient diagnosed with pancreatic cancer. Sections from paraffin- embedded tumors excised from SCID mice revealed typical adenocarcinoma of the pancreas. Karyotypic analysis of cultured cells derived from tumors grown in SCID mice revealed a male karyotype with multiple clonal aberrations: 42, XY, add (3)(p11.2), der(7) t(7;12) (p22;q12), -10, -12, add (14)(p11), -18, add (20)(q13)-22/84, idemx2. Immunostaining of KCI-MOH1 tissues shows strong expression of p53 and p21 proteins. The xenograft model was established by transplanting the KCI-MOH1 cells subcutaneously (sc) in SCID mice. When the sc tumor was transplanted in vivo to other SCID mice, the success rate was 100%, with a doubling time of 8.5 days. The SCID mouse xenograft model was used to test the efficacy of selected standard chemotherapeutic drags (taxol, gemcitabine, 5-fluorouracil, and Ara-C) and novel biological agents (Bryostatin 1 and **Auristatin-PE**). Results show that gemcitabine, Ara-C, and Bryostatin 1 were active against KCI-MOH1. The xenograft described herein can be used as an animal model to facilitate the development of novel therapeutic agents against human pancreatic cancers.

CT Medical Descriptors:
*pancreas tumor
*tumor xenograft
adenocarcinoma
karyotype
clonal anergy
cancer survival
cytogenetics
tumor growth
chromosome aberration
human
nonhuman
male
mouse
case report
animal experiment
animal model
controlled study
aged
conference paper
priority journal
Drug Descriptors:
*taxol: PD, pharmacology
*gemcitabine: PD, pharmacology
*cytarabine: PD, pharmacology
*fluorouracil: PD, pharmacology
*bryostatin 1: PD, pharmacology
protein p53: EC, endogenous compound
protein p21: EC, endogenous compound

RN (taxol) 33069-62-4; (gemcitabine) 103882-84-4; (cytarabine) 147-94-4, 69-74-9; (fluorouracil) 51-21-8; (bryostatin 1) 83314-01-6; (protein p21) 85306-28-1

L36 ANSWER 10 OF 13 EMBASE
on STN
AN 97277531 EMBASE
DN 1997277531
TI Development of new anticancer drugs in Japan - Tubulin-interacting agents.
AU Tsukagoshi S.
CS S. Tsukagoshi, Cancer Institute, Japanese Found. for Cancer Research,

Toshima-ku, Tokyo 170, Japan
SO Japanese Journal of Cancer and Chemotherapy, (1997) 24/SUPPL. 1 (94-99).
Refs: 5
ISSN: 0385-0684 CODEN: GTKRDX
CY Japan
DT Journal; Conference Article
FS 016 Cancer
030 Pharmacology
037 Drug Literature Index
LA English
CT Medical Descriptors:
*cancer chemotherapy
*digestive system cancer: DT, drug therapy
*leukemia
*melanoma
animal cell
animal model
antineoplastic activity
cancer combination chemotherapy
cancer research
clinical trial
conference paper
dose time effect relation
drug research
human
japan
mouse
nonhuman
Drug Descriptors:
*antineoplastic agent: CT, clinical trial
*antineoplastic agent: AN, drug analysis
*antineoplastic agent: CB, drug combination
*antineoplastic agent: DV, drug development
*antineoplastic agent: DT, drug therapy
*dolastatin 10: AN, drug analysis
*dolastatin 10: DV, drug development
*n [2 [(4 hydroxyphenyl)amino] 3 piridinyl] 4 methoxybenzenesulfonamide: AN, drug analysis
*n [2 [(4 hydroxyphenyl)amino] 3 piridinyl] 4 methoxybenzenesulfonamide: DV, drug development
*taxane derivative: DV, drug development
anthracycline antibiotic agent: DV, drug development
antineoplastic antibiotic: DV, drug development
antineoplastic antimetabolite: DV, drug development
cisplatin: DT, drug therapy
cisplatin: CB, drug combination
cisplatin: CT, clinical trial
cytarabine: DV, drug development
fluoropyrimidine: DV, drug development
fluorouracil: CT, clinical trial
fluorouracil: DT, drug therapy
fluorouracil: CB, drug combination
folinic acid: CB, drug combination
methotrexate: CT, clinical trial
methotrexate: CB, drug combination
methotrexate: DT, drug therapy
natural product: DV, drug development
navelbine: DV, drug development
plant extract: DV, drug development
platinum derivative: DV, drug development
taxol: DV, drug development
taxotere: DV, drug development

e 7010
unclassified drug
RN (dolastatin 10) 110417-88-4; (cisplatin) 15663-27-1, 26035-31-4, 96081-74-2; (cytarabine) 147-94-4, 69-74-9; (fluoropyrimidine) 675-21-8; (fluorouracil) 51-21-8; (folinic acid) 58-05-9, 68538-85-2; (methotrexate) 15475-56-6, 59-05-2, 7413-34-5; (navelbine) 71486-22-1; (taxol) 33069-62-4; (taxotere) 114977-28-5
CN **Tzt 1027**; E 7010

L36 ANSWER 11 OF 13 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 97119245 EMBASE
DN 1997119245
TI Antitumour activity of **TZT-1027**, a novel Dolastatin 10 derivative.
AU Kobayashi M.; Natsume T.; Tamaoki S.; Watanabe J.-I.; Asano H.; Mikama T.; Miyasaka K.; Miyazaki K.; Gondo M.; Sakakibara K.; Tsukagoshi S.
CS M. Kobayashi, Pharmacological Research Department, Teikoku Hormone Mfg. Co. Ltd., 1604 Shimosakunobe, Takatsu-ku, Kawasaki 213, Japan
SO Japanese Journal of Cancer Research, (1997) 88/3 (316-327).
Refs: 33
ISSN: 0910-5050 CODEN: JJCREP
CY Japan
DT Journal; Article
FS 016 Cancer
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB Dolastatin 10, a pentapeptide isolated from the marine mollusk Dolabella auricularia, has antitumor activity. **TZT-1027**, a dolastatin 10 derivative, is a newly synthesized antitumor compound. We evaluated its antitumor activity against a variety of transplantable tumors in mice. Intermittent injections of **TZT-1027** were more effective than single or repeated injections in mice with P388 leukemia and B16 melanoma. Consequently, **TZT-1027** shows schedule dependency. **TZT-1027** was effective against P388 leukemia not only when administered i.p., but also when given i.v. However, although **TZT-1027** given i.v. was active against murine solid tumors, **TZT-1027** administered i.p. was ineffective against all the tumors tested with the exception of colon 26 adenocarcinoma. The i.v. injection of **TZT-1027** at a dose of 2.0 mg/kg remarkably inhibited the growth of three murine solid tumors; colon 26 adenocarcinoma, B16 melanoma and M5076 sarcoma, with T/C values of less than 6%. The antitumor activities of **TZT -1027** against these tumors were superior or comparable to those of the reference agents; dolastin 10, cisplatin, vincristine, 5-fluorouracil-resistant P388, but no activity against adriamycin-resistant P388. **TZT-1027** was also effective against human xenografts, that is, tumor regression was observed in mice bearing MX-1 breast and LX-1 lung carcinomas. **TZT-1027** at 10 μM almost completely inhibited the assembly of porcine brain microtubules. Therefore, its mechanism of antitumor action seems to be, at least in part, ascribable to the inhibition of microtubule assembly. Because of its good preclinical activity, **TZT-1027** has been entered into phase I clinical trials.
CT Medical Descriptors:
*antineoplastic activity
animal experiment
animal tissue
article
breast carcinoma
cancer graft

colon adenocarcinoma
controlled study
drug mechanism
drug structure
female
human
human cell
intraperitoneal drug administration
intravenous drug administration
leukemia p 388: DR, drug resistance
lung carcinoma
melanoma b16
microtubule assembly
mouse
nonhuman
oral drug administration
priority journal
sarcoma
swine
tumor regression
tumor xenograft
Drug Descriptors:
*antineoplastic agent: AD, drug administration
*antineoplastic agent: CM, drug comparison
*antineoplastic agent: DV, drug development
*antineoplastic agent: PD, pharmacology
*dolastatin 10: CM, drug comparison
cisplatin: CM, drug comparison
doxorubicin
e 7010: CM, drug comparison
fluorouracil: CM, drug comparison
sulfonamide: CM, drug comparison
tzt 1027: DV, drug development
tzt 1027: PD, pharmacology
tzt 1027: CM, drug comparison
tzt 1027: AD, drug administration
vincristine: CM, drug comparison
unclassified drug

RN (dolastatin 10) 110417-88-4; (cisplatin) 15663-27-1, 26035-31-4, 96081-74-2; (doxorubicin) 23214-92-8, 25316-40-9; (fluorouracil) 51-21-8; (vincristine) 57-22-7

CN **Tzt 1027**; Adriamycin

CO Shionogi (Japan); Bristol myers squibb (Japan); Kyowa hakko kogyo (Japan); Teikoku hormone (Japan)

L36 ANSWER 12 OF 13 EMBASE
on STN

AN 96167211 EMBASE

DN 1996167211

TI Cancer chemotherapy from fundamental and clinical aspects.

AU Tsukagoshi S.

CS Japan

SO Journal of Japan Society for Cancer Therapy, (1996) 31/3 (163-170).
ISSN: 0021-4671 CODEN: NGCJAK

CY Japan

DT Journal; (Short Survey)

FS 016 Cancer
037 Drug Literature Index

LA Japanese

SL English; Japanese

AB Advance in cancer chemotherapy has been greatly supported by the development of new anticancer drugs. Since the clinical efficacies of many anticancer drugs against drug-refractory solid cancers are limited, new

anticancer drugs have to be developed. In the recent clinical studies, novel anticancer drugs such as irinotecan (CPT-11), a topoisomerase I inhibitor, taxol and taxotere, tubulin-interacting drugs, have shown some appreciable activities against human solid cancers. However, in our past experiences, combination of more than two drugs have exhibited better clinical efficacies than monotherapy. Currently methotrexate and 5-fluorouracil (5-FU) sequential therapy and 5-FU and leucovorin based on the concept of biochemical modulation have shown the clinical effects with lesser side effects against cancer of the digestive organs. As for clinical trials, quality of the trials must be considered from many aspects, so that a guideline for the practice of better clinical trial by oncologists has been proposed by the Japan Society for Cancer therapy.

CT Medical Descriptors:
*cancer chemotherapy
clinical trial
combination chemotherapy
drug development
human
short survey
Drug Descriptors:
*fluorouracil
*folic acid
*irinotecan
*methotrexate
*taxol
*taxotere
6 formylamino 12,13 dihydro 1,11 dihydroxy 5h indolo[2,3 a][pyrrolo[3,4 c]carbazole 5,7(6h) dione 13 glucoside
bleomycin
camptothecin
cisplatin
cyclophosphamide
doxorubicin
etoposide
ist 622
navelbine
topotecan
tzt 1027
vinblastine
vincristine
unclassified drug

RN (fluorouracil) 51-21-8; (folic acid) 59-30-3, 6484-89-5; (irinotecan) 100286-90-6; (methotrexate) 15475-56-6, 59-05-2, 7413-34-5; (taxol) 33069-62-4; (taxotere) 114977-28-5; (6 formylamino 12,13 dihydro 1,11 dihydroxy 5h indolo[2,3 a][pyrrolo[3,4 c]carbazole 5,7(6h) dione 13 glucoside) 151069-12-4; (bleomycin) 11056-06-7; (camptothecin) 7689-03-4; (cisplatin) 15663-27-1, 26035-31-4, 96081-74-2; (cyclophosphamide) 50-18-0; (doxorubicin) 23214-92-8, 25316-40-9; (etoposide) 33419-42-0; (navelbine) 71486-22-1; (topotecan) 119413-54-6, 123948-87-8; (vinblastine) 865-21-4; (vincristine) 57-22-7

CN Cpt 11; Nb 506; Ist 622; **Tzt 1027**

L36 ANSWER 13 OF 13 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

AN 95362242 EMBASE

DN 1995362242

TI Antineoplastic agents 337. Synthesis of dolastatin 10 structural modifications.

AU Pettit G.R.; Srirangam J.K.; Barkoczy J.; Williams M.D.; Durkin K.P.M.; Boyd M.R.; Bai R.; Hamel E.; Schmidt J.M.; Chapuis J.-C.

CS Cancer Research Institute, Department of Chemistry, Arizona State University, Box 871604,Tempe, AZ 85287-16-4, United States

SO Anti-Cancer Drug Design, (1995) 10/7 (529-544).

ISSN: 0266-9536 CODEN: ACDDEA
CY United Kingdom
DT Journal; Article
FS 016 Cancer
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB New structural modifications of the marine shell-less mollusk peptide constituent dolastatin 10 (1) have been synthesized, and evaluated against a variety of cancer cell lines and for their ability to inhibit tubulin polymerization. A number of useful structure-activity relationships were uncovered. The most important observation was that the dolaphenine unit of dolastatin 10 could be satisfactorily replaced with a phenethylamine. Peptide 11C, designated **auristatin PE**, was found to exhibit inhibition of cancer cell growth and tubulin assembly comparable to that of dolastatin 10.
CT Medical Descriptors:
*drug structure
*drug synthesis
animal cell
article
cancer cell culture
cancer growth
chemical modification
controlled study
human
human cell
microtubule assembly
mouse
nonhuman
priority journal
structure activity relation
Drug Descriptors:
*antineoplastic agent: AN, drug analysis
*antineoplastic agent: CM, drug comparison
*antineoplastic agent: PD, pharmacology
*dolastatin 10: AN, drug analysis
*dolastatin 10: CM, drug comparison
*dolastatin 10: PD, pharmacology
auristatin pe: AN, drug analysis
auristatin pe: CM, drug comparison
auristatin pe: PD, pharmacology
phenethylamine
tubulin: EC, endogenous compound
unclassified drug
RN (dolastatin 10) 110417-88-4; (phenethylamine) 64-04-0

=> => d all 14 15

L39 ANSWER 14 OF 15 MEDLINE on STN
AN 1999274689 MEDLINE
DN 99274689 PubMed ID: 10341297
TI Induction of growth inhibition and apoptosis in pancreatic cancer cells by **auristatin-PE** and gemcitabine.
AU Li Y; Singh B; Ali N; Sarkar F H
CS Department of Pathology, Karmanos Cancer Institute at Wayne State University School of Medicine, Detroit, MI 48201, USA.
SO INTERNATIONAL JOURNAL OF MOLECULAR MEDICINE, **(1999 Jun)** 3 (6) 647-53.
Journal code: 9810955. ISSN: 1107-3756.
CY Greece

DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199908
ED Entered STN: 19990816
Last Updated on STN: 19990816
Entered Medline: 19990802

AB Pancreatic adenocarcinoma is the fifth leading cause of cancer related deaths in the United States. Treatment for this disease has largely been unsuccessful, which may partly be due to insufficient data regarding the molecular mechanisms of chemotherapeutic drugs currently being used as single agents or in combined modality regimens. In this study, we investigated the molecular mechanisms by which **auristatin-PE**, a newly developed experimental agent, and gemcitabine, a commercially available anti-cancer agent, exert their inhibitory effects on pancreatic cancer cell lines containing wild-type p53 (HPAC) and mutant p53 (PANC-1). Our results showed that **auristatin-PE** and gemcitabine inhibited cell growth and induced cell cycle arrest in G2/M and S phase, respectively. **Auristatin-PE** also induced apoptosis in both cell lines. Western blot analysis showed that **auristatin-PE** up-regulated the expression of wt-p53, p21WAF1 and Bax, and down-regulated Bcl-2 and cyclin B in HPAC cells, while only up-regulation of p21WAF1 and Bax was observed in PANC-1 cells. These results suggest that **auristatin-PE** may induce apoptosis and p21WAF1 expression through p53-dependent or independent pathways, and that up-regulation of p21WAF1 and Bax and down-regulation of Bcl-2 may be the molecular mechanism through which **auristatin-PE** inhibits cell growth and induces apoptosis. Furthermore, the up-regulation of p21WAF1 and down-regulation of cyclin B may contribute to the G2/M cell cycle arrest. Combination of **auristatin-PE** and gemcitabine showed significantly greater inhibition of cell growth and up-regulated expression of p21WAF1 and Bax. From these results, we conclude that the selection of therapeutic agents based on their molecular mechanism may improve therapeutic outcome, and that **auristatin-PE** may be more effective in the treatment of pancreatic cancer when given in combination with gemcitabine, rather than as a single agent.

CT Check Tags: Human; Support, Non-U.S. Gov't
Adenocarcinoma: ME, metabolism
*Adenocarcinoma: PA, pathology
*Antineoplastic Combined Chemotherapy Protocols: PD, pharmacology
*Apoptosis
Blotting, Western
Cell Cycle: DE, drug effects
Cell Division: DE, drug effects
Cyclins: BI, biosynthesis
*Deoxycytidine: AA, analogs & derivatives
Deoxycytidine: PD, pharmacology
Flow Cytometry
Gene Expression: DE, drug effects
*Oligopeptides: PD, pharmacology
Pancreatic Neoplasms: ME, metabolism
*Pancreatic Neoplasms: PA, pathology
Protein p53: BI, biosynthesis
Proto-Oncogene Proteins: BI, biosynthesis
Proto-Oncogene Proteins c-bcl-2: BI, biosynthesis
Tumor Cells, Cultured

RN 103882-84-4 (gemcitabine); **149606-27-9 (TZT 1027)**; 951-77-9 (Deoxycytidine)

CN 0 (Antineoplastic Combined Chemotherapy Protocols); 0 (Bax protein); 0 (Cip1 protein); 0 (Cyclins); 0 (Oligopeptides); 0 (Protein p53); 0 (Proto-Oncogene Proteins); 0 (Proto-Oncogene Proteins c-bcl-2)

L39 ANSWER 15 OF 15 MEDLINE on STN
AN 1999330827 MEDLINE
DN 99330827 PubMed ID: 10402249
TI A new tubulin polymerization inhibitor, **auristatin PE**, induces tumor regression in a human Waldenstrom's macroglobulinemia xenograft model.
AU Mohammad R M; Limvarapuss C; Wall N R; Hamdy N; Beck F W; Pettit G R; Al-Katib A
CS Division of Hematology and Oncology, Wayne State University School of Medicine, Detroit, MI 48201, USA.
NC 1801CA79837 (NCI)
P30CA22453-20 (NCI)
SO INTERNATIONAL JOURNAL OF ONCOLOGY, **(1999 Aug)** 15 (2) 367-72.
Journal code: 9306042. ISSN: 1019-6439.
CY Greece
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199908
ED Entered STN: 19990910
Last Updated on STN: 19990910
Entered Medline: 19990820
AB Waldenstrom's macroglobulinemia (WM) is an uncommon lymphoproliferative disease which remains incurable with current treatment protocols. We have previously established a permanent WM cell line, WSU-WM, which grows as a xenograft in severe combined immune deficient (SCID) mice. In this study, we investigated the anti-tumor effects of **auristatin PE** (a structural modification of the marine, shell-less mollusk peptide constituent dolastatin 10). WSU-WM cells were cultured in RPMI-1640 at a concentration of 2x10(5) cells/ml using 24-well plates. **Auristatin PE** or dolastatin 10 were added to triplicate wells and cell count and viability were assessed after 24, 48 and 72 h. Results showed that both agents were active against WSU-WM, and were able to induce complete growth inhibition at 100 pg/ml. The efficacy of these agents in vivo was evaluated using the WSU-WM SCID mouse xenograft model. **Auristatin PE** and dolastatin 10 were given i.v. via tail vein at 2.0 mg/kg and 0.2 mg/kg, respectively. The agents were given every second day for three injections which represent the maximum tolerated doses. Tumor growth inhibition (T/C), tumor growth delay (T-C), and log10 kill for **auristatin PE** and dolastatin 10 were 0%, 18 days, 2.83 and 67%, 2 days, 0.06, respectively. Based on these animal results, dolastatin 10 was inactive while **auristatin PE** was highly active. We therefore focused further investigation on **auristatin PE** to understand some of its mechanisms of action. Using two flow cytometry assays, propidium iodide for cell cycle analysis and 7-amino actinomycin D (7AAD) to detect apoptosis, we were able to demonstrate that **auristatin PE** at 10 pg/ml after 24 h arrested 50% of WSU-MW cells in G2M. Concomitantly, 31% of **auristatin PE**-treated cells entered apoptosis. By 72 h, greater than 75% of the cells became apoptotic. The activity of **auristatin PE** should be evaluated in other tumor types and in clinical trials.
CT Check Tags: Animal; Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
*Antineoplastic Agents: TU, therapeutic use
Apoptosis: DE, drug effects
Biopolymers
Cell Division: DE, drug effects
Disease Models, Animal
Flow Cytometry
Mice
Mice, SCID
Middle Age

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      Mitosis: DE, drug effects
     *Oligopeptides: TU, therapeutic use
     *Remission Induction: MT, methods
      Severe Combined Immunodeficiency
      Transplantation, Heterologous
     *Tubulin: DE, drug effects
     *Waldenstrom Macroglobulinemia: DT, drug therapy
RN   149606-27-9 (TZT 1027)
CN   0 (Antineoplastic Agents); 0 (Biopolymers); 0 (Oligopeptides); 0 (Tubulin)


=> d his

     (FILE 'HOME' ENTERED AT 08:16:11 ON 11 DEC 2003)
               SET COST OFF

     FILE 'REGISTRY' ENTERED AT 08:16:25 ON 11 DEC 2003
               E TZT/CN
L1             1 S E6
               E C39H67N5O6/MF
L2             7 S E3
L3             3 S L2 AND NC4/ES AND 46.150.18/RID
L4             2 S L3 NOT L1
               SEL RN L1
L5             7 S E1/CRN

     FILE 'HCAOLD' ENTERED AT 08:20:14 ON 11 DEC 2003
L6             0 S L1

     FILE 'HCAPLUS' ENTERED AT 08:20:14 ON 11 DEC 2003
L7            37 S L1
L8            31 S TZT1027 OR TZT 1027 OR SOBLIDOTIN? OR AURISTATIN? PE

     FILE 'HCAOLD' ENTERED AT 08:20:21 ON 11 DEC 2003
L9             0 S L1

     FILE 'HCAPLUS' ENTERED AT 08:20:22 ON 11 DEC 2003
L10           37 S L1
L11           46 S TZT1027 OR TZT 1027 OR SOBLIDOTIN? OR AURISTATIN? PE OR AURIS
L12           53 S L10,L11
L13            9 S L12 AND (KOHNO ? OR WATANABE ?)/AU
L14           21 S L12 AND TEIKOKU?/PA,CS
L15            1 S L12 AND (WO2000-JP2 OR JP99-2971)/AP,PRN

     FILE 'REGISTRY' ENTERED AT 08:47:20 ON 11 DEC 2003
L16            1 S 142243-02-5

     FILE 'HCAPLUS' ENTERED AT 08:48:03 ON 11 DEC 2003
L17         7980 S L16
L18          367 S ERK(A)MAP()KINASE
L19        12817 S MITOGEN ACTIVATED PROTEIN KINASE
L20          699 S EXTRACELLULAR SIGNAL REGULATED PROTEIN KINASE
L21        12557 S MAP KINASE
L22         4309 S EXTRACELLULAR SIGNAL REGULATED KINASE
L23         2526 S ERK KINASE
L24            1 S L12 AND L17-L23
               E ANTITUMOR/CT
               E E5+ALL
L25       165939 S E1,E2
L26        20279 S E25,E26
               E E25+ALL
L27         1545 S E3
L28           40 S L12 AND L25-L27
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L29          53 S L12,L13-L15,L24,L28
L30          20 S L29 AND (PD<=19990108 OR PRD<=19990108 OR AD<=19990108)

     FILE 'REGISTRY' ENTERED AT 08:52:56 ON 11 DEC 2003

     FILE 'HCAPLUS' ENTERED AT 08:53:14 ON 11 DEC 2003

     FILE 'USPATFULL, USPAT2' ENTERED AT 08:53:28 ON 11 DEC 2003
L31           4 S L1
L32          37 S L11
L33          40 S L31,L32
L34           4 S L33 AND (PD<=19990108 OR PRD<=19990108)

     FILE 'USPATFULL, USPAT2' ENTERED AT 08:54:25 ON 11 DEC 2003

     FILE 'EMBASE' ENTERED AT 08:55:04 ON 11 DEC 2003
L35          44 S L1 OR L11
L36          13 S L35 AND PY<=1999

     FILE 'EMBASE' ENTERED AT 08:55:53 ON 11 DEC 2003

     FILE 'MEDLINE' ENTERED AT 08:56:14 ON 11 DEC 2003
L37          34 S L1 OR L11
L38          13 S L37 AND PY<=1999

     FILE 'EMBASE, MEDLINE' ENTERED AT 08:56:41 ON 11 DEC 2003
L39          15 DUP REM L36 L38 (11 DUPLICATES REMOVED)

=> => fil wpix
FILE 'WPIX' ENTERED AT 08:57:45 ON 11 DEC 2003
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FILE LAST UPDATED:          8 DEC 2003      <20031208/UP>
MOST RECENT DERWENT UPDATE:     200379        <200379/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE


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>>> SLART (Simultaneous Left and Right Truncation) is now
    available in the /ABEX field. An additional search field
    /BIX is also provided which comprises both /BI and /ABEX <<<

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    GUIDES, PLEASE VISIT:
    http://thomsonderwent.com/support/userguides/              <<<


=> d all abeq tech abex tot

L40  ANSWER 1 OF 9  WPIX  COPYRIGHT 2003 THOMSON DERWENT on STN
AN   2003-788183 [74]    WPIX
DNN  N2003-631600        DNC C2003-217603
TI   Construction of model for predicting sensitivity to drug based on
```

expression levels of genes, comprising partial least square method type 1 using sensitivity data and at least part of gene expression data.

DC B04 B05 D16 S03 T01

IN AOKI, Y; HASEGAWA, K; ISHII, N; MORI, K

PA (HOFF) HOFFMANN LA ROCHE & CO AG F

CYC 99

PI WO 2003076660 A1 20030918 (200374)* EN 41p C12Q001-68
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW

ADT WO 2003076660 A1 WO 2002-JP2354 20020313

PRAI WO 2002-JP2354 20020313

IC ICM C12Q001-68
ICS G06F017-17; G06K009-62

AB WO2003076660 A UPAB: 20031117
NOVELTY - Construction of a model for predicting sensitivity to drug based on expression levels of genes, comprises partial least square method type 1 using sensitivity data (a) and at least a part of gene expression data (b).

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) selecting genes that contribute to biological sensitivity to a high degree, comprising selecting part or all of the combinations of genes in the model;

(2) a method (M1) for predicting the sensitivity of a test specimen towards a particular stimulus, comprising correlating a high level of expression of a gene having a positive coefficient in the model and a low level of expression of a gene having a negative coefficient in the model for high sensitivities, and a low level of expression of a gene having a positive coefficient in the model and a high level of expression of a gene having a negative coefficient in the model for low sensitivities;

(3) a computer device that predicts the sensitivity of a test specimen towards a particular stimulus comprising:

(i) a device for storing a parameter (model coefficient) representing the relationship between gene expression data and sensitivity value in the model;

(ii) a device for inputting the gene expression data into the model;

(iii) a device for storing the expression data;

(iv) a device for predictively calculating the sensitivity value from (b) and the parameter (model coefficient) based on the model;

(v) a device for storing the predictively calculated sensitivity value; and

(vi) a device for outputting the predictively calculated sensitivity value or a result obtained from the sensitivity value;

(4) producing a high-density nucleic acid array comprising immobilizing or generating, on a support, nucleic acids comprising at least 15 nucleotides comprised in nucleotide sequences encoding the respective genes;

(5) producing a probe or a primer for quantitative or semi-quantitative PCR for respective genes, comprising synthesizing nucleic acids comprising at least 15 nucleotides comprised in nucleotide sequences encoding the respective genes; and

(6) a kit comprising a high-density nucleic acid array, or a probe or primer, and a storage medium for recording the sensitivity to the drugs predicted using the array, or the probe or primer.

USE - For predicting sensitivity (e.g. antitumor effect) to drugs including farnesyltransferase inhibitors (e.g. R-115777, BMS-214662, SCH-66336, L-778123 or 4-(hydroxy-(3-methyl-3H-imidazole-4-yl)-(5-nitro-7-phenyl-benzofuran-2-yl)-methyl)benzonitrile hydrochloride)), fluorinated pyrimidines (e.g. Xeloda (RTM; (1-(3,4-dihydroxy-5-methyl-tetrahydro-furan-2-yl)-5-fluoro-2-oxo-1,2-dihydro-pyrimidin-4-yl)-carbamic acid butyl

ester), Furtulon, 5-Fu (5-fluoro-1H-pyrimidine-2,4-dione), Carmofur, Tegafur and/or UFT (2,4-(1H,3H)-pyrimidinedione), or Tegafur, 5-chloro-2,4-dihydroxypyridine and potassium oxonate), taxanes (e.g. taxol, taxotere, IDN-5109, BMS-188797 or BMS-184476), camptothecins (e.g. camptothecin, CPT-11, Topotecan, DX-8951f, BN-80915, 9-aminocamptothecin or 9-nitrocamptothecin), nucleoside analogue antitumor drugs (e.g. DFDC, DMDC, FMDC, Ara-C, decitabine, troxacitabine, 2-fluoro-9-(5-O-phosphono-beta -D-arabinofuranosyl)-9H-purin-6-amine or cladribine), dolastatins (e.g. dolastatin-10, dolastatin-14, dolastatin-15, **TZT-1027** or cemadotin), anthracyclines (e.g. adriamycin, epirubicin, daunomycin or idarubicin), protein kinase inhibitors (e.g. ZD-1839, CP-358774, PD-158780, GW-2016, SU-5416, SU-6668, PTK-787, ZD-6474, GW-2286, STI-571, CGP-41251, CI-1040 or BAY-439006), platinum antitumor drugs (e.g. cisplatin, carboplatin or BBR-3464), epothilones (e.g. epothilone-D, epothilone or BMX-247550), aromatase inhibitors (e.g. ZD-1033, FCE-24304 or CGS-20267), or hormone modulators (e.g. tamoxifen, LY-156758, LY-353381, EM-800, TAT-59, TZP4238 or leuprorelin, based on expression levels of genes (claimed).

ADVANTAGE - The model predicts the sensitivity of a biological specimen to a specific drug.

Dwg.0/7

FS CPI EPI

FA AB; DCN

MC CPI: B01-B04; B02-A; B02-D; B02-E; B02-I; B04-C01A; B04-C01B; B04-E01; B04-E05; B04-F02A; B04-N06; B05-A01A; B05-A03B; B05-B01M; B05-B01N; B06-H; B07-H; B10-A10; B10-A18; B10-B03B; B11-C08E5; B11-C08E6; B11-C09; B12-K04E; B12-K04F; B14-D01; B14-D02; B14-D06; B14-D10; B14-H01; D05-H09; D05-H12D1; D05-H12D6

EPI: S03-E14A1; T01-J04D; T01-J15H; T01-J16C4

TECH UPTX: 20031117

TECHNOLOGY FOCUS - BIOLOGY - Preferred Method: The model is optimized for each of at least two sets of combinations of genes by the partial least square method type 1 and by selecting those models in which the number of genes is small and/or those models whose predictive correlation coefficient (Q2) value is high. The model is constructed by computing a parameter that represents a degree of contribution for each of the genes and by selecting the genes that have the greater relative parameter, or by generating different combinations of genes based on a genetic algorithm. The parameter representing the degree of contribution is a modeling power value. (a) Comprises in vitro sensitivity data, animal-experimental sensitivity data and clinical sensitivity data for a biological specimen (e.g. cancer cell or a cancer cell line). (b) Comprises high-density nucleic acid array data. (M1) involves obtaining (b) in the model for the test specimen, and computing the sensitivity by applying (b) to the model.

L40 ANSWER 2 OF 9 WPIX COPYRIGHT 2003 THOMSON DERWENT on STN

AN 2003-756783 [71] WPIX

DNC C2003-207731

TI New antibody that competitively inhibits binding of TMEFF219 to TMEFF2, useful for treating prostate cancer, e.g. primary, metastatic, locally advanced, or androgen independent prostate cancer.

DC B04 D16

IN AFAR, D; BHASKAR, V; CARAS, I; DE LA CALLE, A; LAW, D; MURRAY, R; POWERS, D; RAMAKRISHNAN, V

PA (EOSB-N) EOS BIOTECHNOLOGY INC

CYC 103

PI WO 2003075855 A2 20030918 (200371)* EN 31p A61K000-00

RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU

ZA ZM ZW
ADT WO 2003075855 A2 WO 2003-US7209 20030307
PRAI US 2002-436812P 20021227; US 2002-362837P 20020308
IC ICM A61K000-00
AB WO2003075855 A UPAB: 20031105
NOVELTY - An antibody that competitively inhibits binding of TMEFF219 to TMEFF2, is new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:
(1) a pharmaceutical composition comprising the antibody and a carrier;
(2) detecting a prostate cancer cell in a biological sample from a patient by contacting the biological sample with the antibody;
(3) inhibiting proliferation of a prostate cancer-associated cell by contacting the cell with the antibody; and
(4) treating prostate cancer with an antibody to TMEFF2.
ACTIVITY - Cytostatic. No biological data given.
MECHANISM OF ACTION - Vaccine.
USE - The antibody, composition and method are useful for treating prostate cancer, e.g. primary prostate cancer, metastatic prostate cancer, locally advanced prostate cancer, androgen independent prostate cancer, prostate cancer that has been treated with neoadjuvant therapy, or prostate cancer that is refractory to treatment with neoadjuvant therapy (claimed).
Dwg.0/0
FS CPI
FA AB; DCN
MC CPI: B04-B04C2; B04-B04G; B04-C01G; B04-E03A; B04-F02A; B04-G05; B04-P01; B11-C07A3; B11-C07A5; B11-C07A6; B12-K04A1; D05-H08; D05-H09; D05-H11; D05-H12A; D05-H13
TECH UPTX: 20031105
TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Antibody: The antibody is further conjugated to an effector component selected from a fluorescent label, a radioisotope or a cytotoxic chemical. The cytotoxic chemical is **auristatin**. The antibody is selected from an antibody fragment, humanized antibody, and TMEFF219. The TMEFF2 is on a cancer cell. Preferred Method: In detecting a prostate cancer cell in a biological sample from a patient, the antibody is further conjugated to a fluorescent label. In inhibiting proliferation of a prostate cancer-associated cell, the antibody is an antibody fragment. The prostate cancer cell is in a patient, preferably a primate. The patient is undergoing a therapeutic regimen to treat metastatic prostate cancer, or suspected of having metastatic prostate cancer.
ABEX UPTX: 20031105
SPECIFIC SEQUENCES - Specifically claimed are the TMEFF219 antibody heavy and light chain variable regions comprising any of the 7 amino acid sequences of 108 or 120 aa or their encoding DNA comprising any of the 7 nucleotide sequences of 324 or 360 bp fully defined in (table 2) in the specification.

ADMINISTRATION - Administration is oral, subcutaneous, intravenous, intranasal, transdermal, intraperitoneal, intramuscular, intrapulmonary, vaginal, rectal or intraocular. No dosage is given.

EXAMPLE - No relevant example given.

L40 ANSWER 3 OF 9 WPIX COPYRIGHT 2003 THOMSON DERWENT on STN
AN 2003-468727 [44] WPIX
DNC C2003-125179
TI Treating immunological disorder that is not cancer, in a subject, by administering composition comprising a first antibody that specifically binds CD30 and exerts a cytostatic or cytotoxic effect on activated lymphocyte.

DC B04 D16
IN DORONINA, S; KLUSSMAN, K; LAW, C; SENTER, P; TOKI, B; WAHL, A F
PA (SEAT-N) SEATTLE GENETICS INC
CYC 100
PI WO 2003043583 A2 20030530 (200344)* EN 194p A61K000-00
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW
ADT WO 2003043583 A2 WO 2002-US37223 20021120
PRAI US 2001-331750P 20011120
IC ICM A61K000-00
AB WO2003043583 A UPAB: 20030710
NOVELTY - Treating (M1) an immunological disorder in a subject, where the immunological disorder is not cancer, involves administering to the subject, a pharmaceutical composition comprising a first antibody (I) that immunospecifically binds CD30 and exerts a cytostatic or cytotoxic effect on an activated lymphocyte, and a carrier.

DETAILED DESCRIPTION - Treating (M1) an immunological disorder in a subject, where the immunological disorder is not cancer, involves administering to the subject, a pharmaceutical composition comprising a first antibody (I) that immunospecifically binds CD30 and exerts a cytostatic or cytotoxic effect on an activated lymphocyte, and a carrier. (I) induces CD30 signaling in a lymphocyte, and competes for binding to CD30 with mono- clonal antibodies AC10 or HeFi-1. (I) comprises a fully defined AC10 heavy chain variable region sequence of 117 amino acids as given in specification, comprises 1, 2 or all of Asp-Tyr-Tyr-Ile- Thr, Trp-Ile-Tyr-Pro-Gly-Ser-Gly-Asn-Thr-Lys- Tyr-Asn-Glu-Lys-Phe-Lys-Gly and Tyr-Gly-Asn-Tyr-Trp-Phe-Ala-Tyr, which are the heavy chain complementarity determining region (CDR)1, CDR2 and CDR3 sequences of AC10 heavy chain, respectively. Optionally, (I) comprises a fully defined HeFi-1 heavy chain variable region sequence of 125 amino acids as given in specification, and comprises one, two or all of Asp-Tyr-Tyr-Met-Asn, Phe-Ile-Arg-Asn-Lys-Ala-Asn-Gly-Tyr-Thr-Thr- Glu-Phe-Ser-Ala-Ser-Val-Met-Gly and Asp-Pro-Pro-Tyr-Gly-Asn-Pro- His-Tyr-Tyr-Ala-Met-Asp-Tyr which are the heavy chain CDR1, CDR2 and CDR3 sequences of HeFi-1 heavy chain, respectively.

ACTIVITY - Dermatological; Immunosuppressive; Antiinflammatory; Antiasthmatic; Ophthalmological; Antiallergic; Anti- rheumatic; Antiarthritic; Antipsoriatic; Neuroprotective; Thyromimetic; Antithyroid; Hepatotrophic; Vasotropic; Tuberculostatic; Virucide; Anti-HIV.

MECHANISM OF ACTION - Inducer of apoptosis; Kills or inhibits the growth of activated lymphocytes. Four micro g/ml of the anti-CD30 mAb AC10 or HeFi-1 were mixed with F(ab')2 fragments of goat antimouse (GAM) IgG Fc at final ratios (weight:weight) of 1:4 in culture medium (RPMI-1640, 10% fetal bovine serum (FBS), 2 mM L-glutamine, 1 mM sodium pyruvate, and 0.1 mM non-essential amino acids. The antibody cocktails were allowed to incubate at room temperature for 15 minutes. Serial 1:10 dilutions of these antibody cocktails in culture medium were then prepared. One ml of antibody cocktails was then mixed with 1 ml of Jurkat cell suspension containing 0.25 multiply 106 cells in 12- well tissue culture (TC) plates. After 24 or 48 hours of incubation, cells were harvested by centrifugation and resuspended in 2 ml of fresh medium equilibrated at 37 deg. C. Bromodeoxyuridine (BrdU) was used to label cells that were actively synthesizing DNA. To the labeled cells, 25 micro l of fluorescein isothiocyanate (FITC) labeled anti-BrdU were added, and the cell suspension were incubated at room temperature for 30 minutes. Cells were then washed twice with phosphate buffered saline (PBS), 0.5% Tween 20, 1% bovine serum albumin (BSA), and then resuspended in 0.5 ml of PBS containing 5 micro g/ml of propidium iodide (PI) to quantify DNA contents

in cells. DNA synthesis and cell cycle status were then examined by flow cytometry. DNA fragmentation (characteristic of apoptosis) was detectable after 24 and 48 hours of incubation. These data suggest that the inhibition of proliferation of Jurkat cells was accompanied by cells undergoing apoptosis in response to CD30 signaling. When the percentages of cells in different parts of the cell cycle from cultures treated with graded doses of AC10 and HeFi-1 were compiled, it was evident that AC10 or HeFi-1 at concentrations of greater than 0.002 micro g/ml were able to induce substantial apoptosis in Jurkat cells, especially after 48 hours of treatment. The appearance of apoptotic cells was paralleled by a corresponding decrease in the percentages of cells in the G0/G1, S, and G2/M phases of the cell cycle.

USE - (M1) is useful for treating an immunological disorder in a subject, where the immunological disorder is not cancer. The method is useful for treating a Th2-lymphocyte related disorder such as atopic dermatitis, systemic lupus erythematosus, atopic asthma, rhinoconjunctivitis, allergic rhinitis, Omenn's syndrome, systemic sclerosis, or chronic graft-versus-host disease. The method is also useful for treating a Th1-lymphocyte-related immunological disorder such as rheumatoid arthritis, multiple sclerosis, psoriasis, Sjogren's syndrome, Hashimoto's thyroiditis, Grave's disease, primary biliary cirrhosis, Wegener's granulomatosis, tuberculosis, or acute graft-versus-host disease, or for treating an immunological disorder due to viral infection that involves Epstein-Barr virus, HIV, human T leukemia virus, hepatitis B virus or measles virus, or for treating an activated B lymphocyte-related disorder (claimed).

Dwg.0/23

FS CPI

FA AB; DCN

MC CPI: B01-B01; B01-B02; B02-C01; B04-N08; B06-A03; B06-D09; B06-D18; B06-E05; B07-D03; B07-F01; D05-H08; D05-H11

TECH UPTX: 20030710

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Method: (I) is capable of exerting the cytotoxic or cytostatic effect without conjugation to a cytotoxic agent. (I) is also capable of exerting the cytotoxic or cytostatic effect in the absence of cells other than the activated lymphocyte and of exerting the cytotoxic or cytostatic effect as a monospecific antibody. (I) is a bispecific antibody, which binds to CD30 and a second receptor or receptor complex expressed on activated lymphocytes. The portion of the bispecific antibody that binds to the second receptor or receptor complex enhances the cytostatic or cytotoxic effect of the portion of the bispecific antibody that binds to CD30, and the binding of the bispecific antibody to the second receptor or receptor complex enhances the cytostatic or cytotoxic effect of the of the portion of the bispecific antibody that binds to CD30 by delivering a signal to the activated lymphocyte. (I) is a fusion protein comprises the amino acid sequence of a second protein that is not an antibody. The second protein confers multivalent binding properties to the (I). (I) is conjugated to a cytotoxic agent e.g. enediyne, lexitropsin, duocarmycin, taxane, puromycin; paclitaxel, docetaxel, CC- 1065, SN-38, topotecan, morpholino-doxorubicin, rhizoxin; an anti-tubulin agent such as vinca alkaloid, podophyllotoxin, taxane, baccatin derivative, cryptophysin, maytansinoid, combretastatin, dolastatin, vincristine, vinblastine, vindesine, vinorelbine, VP-16, camptothecin, paclitaxel, docetaxel, epithilone A; monomethyl **auristatin** E (MMAE); or dimethylvaline-valine-dolaiso- leucine-dolaproline-phenylalanine-p-phenylenediamine (AEFP). (I) is conjugated to the cytotoxic agent through a peptide linker such as val-cit linker or a phe-lys linker, hydrazone-linker or a disulfide-linker. The conjugate is preferably cAC10-val-cit-MMAE, or cAC10-val-cit-AEFP. The linker (preferably a hydrazone linker or a disulfide linker) is hydrolyzable at a pH of less than 5.5, preferably less than 5.0. (I) is conjugated to the cytotoxic agent through a (peptide) linker or peptide linker, where the linker is

cleavable by a protease, a membrane associated protease, intracellular protease, endosomal protease or lysosomal protease. (I) is a monoclonal, chimeric, human, humanized, glycosylated, multispecific or single-chain antibody, or is a Fab, F(ab') or F(ab')2 fragment, Fd, a single-chain Fv, disulfide-linked Fv, a fragment comprising a VL domain, a polypeptide that binds specifically to CD30, or a fragment comprising a VH domain. Preferably, (I) is a multivalent human, humanized or chimeric antibody. (M1) further involves administering an agent that potentiates the cytostatic or cytotoxic effect of the (I), or administering a second antibody that enhances the cytostatic or cytotoxic effect of (I) by delivering a signal to the activated lymphocyte. The second antibody recognizes a second receptor or receptor complex expressed on activated lymphocytes. The receptor or the receptor complex comprises an immunoglobulin gene superfamily member (e.g., CD2, CD3, CD4, CD8, CD19, etc.), a TNF-receptor superfamily member (CD27, CD40, CD95/Fas, CD134/OX40, CD137/4- 1BB, etc), an integrin (CD11a, CD11b, CD11c, CD18, CD29, etc.), a cytokine receptor, a chemokine receptor, a major histocompatibility protein, a lectin (C-type, S-type, or I-type lectin), or a complement control protein. (M1) further comprises administering a ligand that binds to a receptor or receptor complex expressed on activated lymphocytes. The ligand enhances the cytostatic or cytotoxic effect of (I) by delivering a signal to the activated lymphocyte. (M1) further comprises administering an immunosuppressive agent such as ganciclovir, etanercept, cyclosporine, tacrolimus, or rapamycin. The immunosuppressive agent is an alkylating agent (e.g. cyclophosphamide), antimetabolite (e.g. a purine antagonist such as azathioprine, or mycophenolate mofetil; or dihydrofolate reductase inhibitor such as methotrexate), glucocorticoid (e.g. cortisol or aldosterone), glucocorticoid analog (e.g. prednisone or dexamethasone), or anti-inflammatory agent (e.g. cyclooxygenase inhibitor, a 5-lipoxygenase inhibitor, or leukotriene receptor antagonist).

ABEX UPTX: 20030710

WIDER DISCLOSURE - The following are also disclosed as new:
(1) use of proteins (e.g. antibodies) that bind to CD30 and induce CD30 signaling in a lymphocyte and/or exert a cytostatic or cytotoxic effect on an activated lymphocyte to treat or prevent immunological disorders;
(2) use of proteins that compete with AC10 or HeFi-1 for binding to CD30 and induce CD30 signaling in a lymphocyte and/or exert a cytostatic or cytotoxic effect on activated lymphocytes;
(3) use of fragments and other derivatives and analogs of such AC10 and HeFi-1 proteins, and nucleic acids encoding the proteins, fragments or derivatives (including fusion proteins) to treat or prevent immunological disorders; and
(4) pharmaceutical compositions comprising the antibodies.

ADMINISTRATION - The pharmaceutical compositions are administered by inhalation or insufflation, or oral, buccal, parenteral or rectal route. Dosages range from 0.1-100 (prefer- ably, 1-10) mg/kg of patient's body weight.

L40 ANSWER 4 OF 9 WPIX COPYRIGHT 2003 THOMSON DERWENT on STN
AN 2003-449100 [42] WPIX
DNC C2003-119127
TI New drug-ligand conjugates useful as prodrugs for the delivery of drugs to cell populations for treating e.g. cancer.
DC B05
IN SENTER, P D; TOKI, B E
PA (SEAT-N) SEATTLE GENETICS INC; (SENT-I) SENTER P D; (TOKI-I) TOKI B E
CYC 100
PI WO 2003026577 A2 20030403 (200342)* EN 55p A61K000-00
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR

KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW

US 2003096743 A1 20030522 (200342) A61K038-16
US 2003130189 A1 20030710 (200347) A61K038-16

ADT WO 2003026577 A2 WO 2002-US30282 20020924; US 2003096743 A1 US 2001-963103 20010924; US 2003130189 A1 CIP of US 2001-963103 20010924, US 2002-252947 20020923

PRAI US 2002-252947 20020923; US 2001-963103 20010924

IC ICM A61K000-00; A61K038-16
ICS A61K031-165; A61K031-401; A61K031-405; A61K031-4172; A61K031-4178; C07K014-00

AB WO2003026577 A UPAB: 20030703
NOVELTY - Drug-ligand conjugates are new.
DETAILED DESCRIPTION - Drug conjugates (C1) of formula L-(An-Z-X-W'w-)-D (I) and B'-(Z-X-W'w)-D (II) are new.
D = a drug group;
L = ligand;
A = an optional acyl unit;
Z = an amino acid or peptide;
X = aminobenzyl ether self-immolative group;
W' = optional second self-immolative group;
n = 0 or 1;
w = n; and
B' = blocking group.
ACTIVITY - Cytostatic; Immunosuppressive; Dermatological; Antiasthmatic; Ophthalmological; Antiinflammatory; Antirheumatic; Antiarthritic; Neuroprotective; Antipsoriatic; Thyromimetic; Antithyroid; Hepatotropic; Tuberculostatic; Antidiabetic; Antibacterial; Fungicide; Antiparasitic; Virucide; Protozoacide; Antipyretic; Anti-HIV; Nephrotropic.
Test details are given but no results are described.
MECHANISM OF ACTION - Cell proliferation inhibitor.
USE - As prodrugs for the delivery of drugs to cell populations for treating e.g. cancer; for reducing cellular proliferation; for treating disease in which intracellular enzymes are released or are made accessible by cell damage, and an undesirable biological condition in mammal (claimed); for treating autoimmune diseases e.g. atopic dermatitis, atopic asthma, rhinoconjunctivitis, allergic rhinitis, Omenn's syndrome, systemic sclerosis, graft versus host disease, rheumatoid arthritis, multiple sclerosis, psoriasis, Sjoegren's syndrome, Hashimoto's thyroiditis, Grave's disease, primary biliary cirrhosis, Wegener's granulomatosis, tuberculosis, systemic lupus erythematosus, Goodpasture's syndrome, type I diabetes; for treating bacterial diseases (e.g. pneumonia, ecthyma, endocarditis, septic arthritis, proctitis, sinusitis, Lyme disease, leprosy and inclusion conjunctivitis), fungal disease (e.g. histoplamosis, sporotrichosis, mycetoma and chromomycosis), rickettsial disease (e.g. ehrlichiosis, Q fever and bartonellosis), parasitic disease (e.g. malaria, dum-dum fever, ascariasis and tapeworm infections), and viral disease (e.g. influenza, common cold, AIDS, rabies, smallpox and bronchitis). The cancer treatment includes treatment of ovarian, CNS, renal, lung, colon, melanoma and hematologic cancers or tumors.
ADVANTAGE - (C1) has high serum stability and conditional drug release upon peptide bond hydrolysis.
Dwg.0/2

FS CPI

FA AB; GI; DCN

MC CPI: B02-M; B02-R; B02-T; B04-B04D2; B04-C01A; B04-C01C; B04-C02C; B04-C02E3; B04-C03; B04-C03B; B04-D01; B04-G2100E; B04-H02B; B04-H02G; B04-H06; B04-H06B; B04-H06F; B04-H06H; B04-N04; B06-A01; B06-A02; B06-A03; B06-D01; B06-D09; B06-D16; B06-E05; B07-D12; B08-D02; B10-A19; B10-B03A; B10-B04B; B10-D03; B10-E02; B10-E04C; B14-A01; B14-A01A7; B14-A01B1; B14-A01B2; B14-A02; B14-A02A4;

B14-A02B3; B14-A02B4; B14-A03B; B14-B02; B14-C09B; B14-G02A; B14-G02C; B14-G02D; B14-H01; B14-K01A; B14-N03; B14-N04; B14-N11; B14-N12; B14-N17C; B14-S01; B14-S04

TECH UPTX: 20030703

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: (C1) is prepared by dissolving a peptide derivative, triphenylphosphine and respective phenol in dimethylformamide (DMF)/toluene and then evaporated to dryness. The residue was treated with DMF under nitrogen, cooled and diisopropyl azodicarboxylate (DIAD) was added to give the conjugate.

Preferred Conjugate: (C1) is of formula (Ia), (Ib), (IIa) or (IIb).

O-D = a portion of drug where the drug has formula HO-D (where O is bonded to C atom that forms an aromatic ring of D or to an aliphatic C atom of D);

J = a substituent group (preferably an electron-withdrawing group selected from F, Cl, Br, CN, CF3, CONH2, CHO, CO2CH3, COCH3, NHCOCH3, NO2 or sulfonyl group);

m = 0 - 4 (preferably 0 or 1);

D' = drug comprising T group;

T = O, S, NH or N(lower alkyl);

A' = acyl unit;

p = 1 or 2;

R1 - R4 = H or 1-5C alkyl; and

B'' = H or blocking group selected from a D-amino acid and N-terminus protecting group (preferably carbobenzoxy protecting group).

The groups L-A'n-Z-C(=O)-NH- and B''-Z-C(=O)-NH- are situated at an ortho- or para- positions (preferably para-positions) with respect to the respective -CH2 groups. The HO-D has a pKa of at most 16.

ABEX UPTX: 20030703

ADMINISTRATION - (C1) is administered orally, topically, parenterally (including subcutaneously, intravenously, intramuscularly, intrasternally or by infusion), sublingually, rectally, vaginally, ocularly or intranasally. No dosage given.

EXAMPLE - Cbz-valine-citrulline-para-aminobenzyl (PAB)alcohol (1 equivalent (eq.)), triphenylphosphine (1.1 eq.) and 1-naphthol (1 - 1.1 eq.) were dissolved in dimethylformamide (DMF)/toluene (1:1) and evaporated to dryness under high vacuum. The residue was treated with dry DMF under nitrogen and cooled to 0 degrees C. Diisopropyl azodicarboxylate (DIAD) (1.1 eq.) was added dropwise over 1 minute with stirring. An additional PPh3 (1.1 eq.) and DIAD was added after 4 hours. The solution was stirred for 16 - 24 hours, followed by solvent removal in vacuo to give the conjugate Cbz-Val-Cit-PAB-1-O-naphthol.

DEFINITIONS - Preferred Definitions:

A = pyrrolidine-2,5-dion-1,3-diyl-(CH2)qC(=O)-;

q = 1 - 10 (preferably 5);

Z = valine-citrulline or phenylalanine-lysine;

n = 1;

D = **auristatin** E, 1,2,9,9a-tetra-hydro-cyclopropa(c)benz(e)indol-4-one (CBI), cyclopropapyrroloindole (CPI) or 1,2,9,9a-tetra-hydro-cyclopropa(c)pyrido(3,2-e)indol-4-one (CPyI) conjugated to a minor groove binder; U-76,073, seco-adozelesin, bizelesin, 1,2,9,9a-tetra-hydro-cyclopropa(c)benz(e)indol-4-one trimethoxyindole (CBI-TMI), duocarmycin C2, duocarmycin B2, seco-CC-1065, pancratistatin, carminomycin, streptonigrin, zorubicin, elliptinium acetate, mitoxantrone, daunorubicin, phenol mustard, doxorubicin, etoposide, combretastatin A-4 or 7-ethyl-10-hydroxycamptothecin (SN-38), mitomycin-C, mitomycin-A, daunorubicin, doxorubicin, N-(5,5-diacetoxypentyl)doxorubicin, aminopterin, actinomycin, bleomycin, 9-amino camptothecin, N8-acetyl spermidine, 1-(2 chloroethyl)-1,2-dimethanesulfonyl hydrazide, tallysomycin and their derivatives, etoposide, camptothecin, taxol, esperamicin, 1,8-dihydroxy-bicyclo(7.3.1)trideca-4,9-diene-2,6-diyne-13-one, anguidine, doxorubicin, morpholino-doxorubicin, N-(5,5-

diacetoxypentyl)doxorubicin, vincristine, vinblastine or their derivatives), esperamicin, 6-mercaptopurine or their derivatives; and L = immunoglobulin such as mAb (selected from BR96, herceptin, rituxan, CD70, S2C6 and AC10), their an antigen-binding fragment, bombesin, EDG, transferrin, gastrin, platelet-derived growth factor, IL-2, IL-6, TFG-alpha, TFG-beta, VGF, insulin, insulin-like growth factors I and II, lectin or apoprotein from low-density lipoproteins, gastrin-releasing peptide, carbohydrate, (hydroxypropyl)methacrylamide, chitin, dextran or styrene-co-maleic acid/anhydride, poly(ethylene glycol), poly(propylene glycol), polyglutamic acid or polylysine.

L40 ANSWER 5 OF 9 WPIX COPYRIGHT 2003 THOMSON DERWENT on STN
AN 2003-403281 [38] WPIX
DNN N2003-321626 DNC C2003-107472
TI Novel isolated antibody which binds to epitope on prostate specific membrane antigen, and competitively inhibits binding of second antibody to its target epitope on the antigen, useful for treating prostate cancer.
DC B04 D16 K08 P31 S03
IN DONOVAN, G P; GARDNER, J; MA, D; MADDON, P J; OLSON, W C; SCHUELKE, N
PA (PSMA-N) PSMA DEV CO LLC
CYC 100
PI WO 2003034903 A2 20030501 (200338)* EN 238p A61B000-00
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZW
ADT WO 2003034903 A2 WO 2002-US33944 20021023
PRAI US 2002-412618P 20020920; US 2001-335215P 20011023; US 2002-362747P 20020307
IC ICM A61B000-00
AB WO2003034903 A UPAB: 20030616
NOVELTY - An isolated antibody (I) (Ab) or its antigen-binding fragment which (a) specifically binds to epitope on prostate specific membrane antigen (PSMA), and competitively inhibits the specific binding of a second (Ab) to its target epitope on PSMA, or (b) specifically binds to epitope on PSMA defined by a second (Ab), is new. All sequence information is fully defined in the specification.

DETAILED DESCRIPTION - An isolated (Ab) (I) or its antigen-binding fragment (a) specifically binds to epitope on prostate specific membrane antigen (PSMA), and competitively inhibits the specific binding of a second (Ab) to its target epitope on PSMA, or (b) specifically binds to epitope on PSMA defined by a second (Ab). The second (Ab) is chosen from a group comprising of the following and fully listed in the specification PSMA 3.7, PSMA 3.8, PSMA 3.9, PSMA 3.11, Abgenix 4.248.2, Abgenix 4.360.3, Abgenix 4.7.1, Abgenix 4.4.1, Abgenix 4.177.3, Abgenix 4.16.1, and antibodies comprising (i) a heavy chain encoded by a nucleic acid molecule comprising the coding region or regions of a nucleotide sequence chosen from sequences of 7570, 7597, 7579, 7558, 7576, or 7561 (S1-S6) nucleotides, and (ii) a light chain encoded by a nucleic acid molecule comprising the coding region or regions of a nucleotide sequence chosen from the sequences of 6082, 6082, 6082, 6085, 6097 or 6094 (S7-S12) nucleotides.

INDEPENDENT CLAIMS are also included for the following:

(1) isolated antigen-binding fragment (II) which comprises CDR of an antigen-binding fragment (of (I)) comprises:

(a) heavy chain variable region encoded by nucleic acid molecule with coding regions chosen from 481, 508, 492, 469 and 487 nucleotides; and

(b) light chain variable region encoded by a nucleic acid molecule comprising coding regions chosen from 463, 463, 463, 466 and 478, where the heavy chain variable region comprises an amino acid sequence chosen from 142, 143, 145, 138 and 144 amino acids and light chain variable

region comprises an amino acid sequence chosen from 127, 127, 127, 128 and 132 amino acids;

(2) expression vector (III) comprising an isolated nucleic acid molecule encoding (I) or (II);

(3) host cell (IV) transformed or transfected by (III);

(4) plasmid (V) which produces (I) or (II);

(5) hybridoma cell (VI) line that produces (I) chosen from PSMA 3.7, PSMA 3.8, PSMA 3.9, PSMA 3.11, PSMA 5.4, PSMA 7.1, PSMA 7.3, PSMA 10.3, PSMA 1.8.3, PSMA A3.1.3, PSMA A3.3.1, Abgenix 4.248.2, Abgenix 4.360.3, Abgenix 4.7.1, Abgenix 4.4.1, Abgenix 4.177.3, Abgenix 4.16.1, Abgenix 4.22.3, Abgenix 4.28.3, Abgenix 4.40.2, Abgenix 4.48.3, Abgenix 4.49.1, Abgenix 4.209.3, Abgenix 4.219.3, Abgenix 4.288.1, Abgenix 4.333.1, Abgenix 4.54.1, Abgenix 4.153.1, Abgenix 4.232.3, Abgenix 4.292.3, Abgenix 4.304.1, Abgenix 4.78.1, Abgenix 4.152.1;

(6) composition (VII) comprising (I) or (II) and a carrier, excipient or stabilizer;

(7) composition (VIII) comprising a combination of two or more (I) or (II), and a carrier, excipient, or stabilizer, where the (Ab) is optionally labeled with a label, radioisotope or therapeutic moiety;

(8) kit for detecting prostate cancer for diagnosis, prognosis or monitoring, comprising (I) bound to a label and one or more compounds for detecting the label;

(9) isolated (Ab) which specifically binds to an epitope on prostate specific membrane antigen, where the (Ab) is encoded by a nucleic acid molecule comprising a nucleotide sequence that is at least about 90% identical to the nucleotide sequence encoding (I) that specifically binds to epitope on PSMA defined by a second (Ab);

(10) isolated (Ab) (IX) or its antigen-binding fragment that selectively binds a PSMA protein multimer, where the isolated (Ab) inhibits or enhances at least one enzymatic activity of the PSMA protein multimer;

(11) composition (X) comprising (IX) and an immunostimulatory oligonucleotide or a cytokine, where (IX) is prepared by immunizing an animal with a preparation comprising a PSMA protein multimer; a composition (XI) comprising an isolated PSMA multimer;

(12) isolated recombinant soluble PSMA (rsPSMA) protein multimer (XII), e.g., rsPSMA protein dimer;

(13) screening for a candidate agent that inhibits or enhances at least one enzymatic activity of a PSMA using an isolated PSMA protein multimer;

(14) candidate agent that inhibits or enhances at least one enzymatic activity of PSMA identified by the above method;

(15) identifying a compound that promotes dissociation of PSMA dimers, using PSMA dimers; and

(16) treating or preventing a PSMA-mediated disease comprising: administering to a subject having PSMA-mediated disease or at risk of having a PSMA-mediated disease an amount of (I) or (II).

ACTIVITY - Cytostatic. Details of test given, but no results are stated.

MECHANISM OF ACTION - Immune response inducer; Mediates cytolysis of cells expressing PSMA; Inhibits the growth of cells expressing PSMA.

USE - (I) is useful for detecting PSMA, or a cell expressing PSMA, diagnosing a PSMA-mediated disease in a subject, assessing the prognosis of a subject with a PSMA-mediated disease, assessing the effectiveness of a treatment of a subject with a PSMA-mediated disease, inhibiting the growth of a cell expressing PSMA, inducing cytolysis of a cell expressing PSMA, treating or preventing a PSMA-mediated disease such as prostate cancer or non-prostate cancer bladder chosen from cancer including transitional cell carcinoma, pancreatic cancer including pancreatic duct carcinoma, lung cancer including non-small cell lung carcinoma, kidney cancer including conventional renal cell carcinoma, sarcoma including soft tissue sarcoma, breast cancer including breast carcinoma, brain cancer including glioblastoma multiforme, neuroendocrine carcinoma, colon cancer

including colonic carcinoma, testicular cancer including testicular embryonal carcinoma, or melanoma including malignant melanoma. (I) is also useful for inhibiting or enhancing folate hydrolase activity of a folate hydrolase polypeptide, inhibiting or enhancing N-acetylated alpha -linked acidic dipeptidase (NLADase) activity of NLADase polypeptide, inhibiting or enhancing dipeptidyl dipeptidase IV activity of a dipeptidyl dipeptidase IV polypeptide, inhibiting or enhancing gamma -glutamyl hydrolase activity of a gamma -glutamyl hydrolase polypeptide, and specific delivery of at least one therapeutic agent to PSMA-expressing cells. (IX), (X) or (XI) is useful for inducing an immune response in a subject in need of such treatment (all claimed).

ADVANTAGE - Since the anti-PSMA antibodies or antigen-binding fragments preferentially target prostate cancer cells, other tissues are spared, As a result, treatment with such biological agents is safer, particularly for elderly patients. Treatment using (I) is effective, because it directs high levels of anti-PSMA antibodies or antigen-binding fragments to the bone marrow and lymph nodes where prostate cancer metastases predominate.

Dwg.0/36

FS CPI EPI GMPI

FA AB; DCN

MC CPI: B04-E03A; B04-E03F; B04-E03G; B04-E08; B04-F0100E; B04-F02A; B04-F05; B04-G05; B04-L01; B04-L05; B11-C07; B12-K04A; B12-K04E; B14-H01; D05-H08; D05-H09; D05-H11; D05-H12A; D05-H12E; D05-H13; D05-H14; K09-B; K09-E

EPI: S03-E14H5; S03-E14H6

TECH UPTX: 20030616

TECHNOLOGY FOCUS - BIOTECHNOLOGY - Preferred Plasmid: (V) is chosen from AB-PG-XG1-006 Heavy Chain, AB-PG1-XG1-006 Light Chain, AB-PG1-XG1-026 Heavy Chain, AB-PG1-XG1-026 Light Chain, AB-PG1-XG1-051 Heavy Chain, AB-PG1-XG1-051 Light Chain, AB-PG1-XG1-069 Heavy Chain, AB-PG1-XG1-069 Light Chain, AB-PG1-XG1-077 Heavy Chain, AB-PG1-XG1-077 Light Chain, PSMA 10.3 Heavy Chain, and PSMA 10.3 Kappa having fully defined sequences as given in the specification.

Preferred Antibody: (I) is selected for its ability to bind live cells such as a tumor cell, preferably a prostate tumor cell such as LNCaP cell. (I) mediates cytolysis of cells expressing PSMA, where the cytolysis of cells expressing PSMA is mediated by effector cells, or is complement-mediated in the presence of effector cells. (I) inhibits the growth of cells expressing PSMA. (I) does not require cell lysis to bind to the epitope on PSMA.

Preferred Method: The PSMA enzyme is chosen from folate hydrolase, NLADase, dipeptidyl dipeptidase IV activity, gamma-glutamyl hydrolase. In the method of 15, (I) or (II) is bound to at least one therapeutic moiety which is a cytotoxic drug, a drug which acts on the tumor neovasculature and combinations of the two. The drug is selected from the group of: calicheamicin, esperamicin, methotrexate, doxorubicin, melphalan, chlorambucil, ARA-C, vindesine, mitomycin C, cis-platinum, etoposide, bleomycin, 5-fluoroacil, estramustine, vincristine, etoposide, doxorubicin, paclitaxel, docetaxel, dolastatin 10, **auristatin** E and **auristatin** PHE. (I) or (II) are bound to a radioisotope, where the radiations emitted by the radioisotope is selected from the group consisting of alpha, beta and gamma radiations. The radioisotope is selected from 225Ac, 212Bi, 213Bi, 186Rh, 177Lu, 90Y, 131I, 67Cu, 125I, 77Br, 153Sm, 166Ho, 64Cu, 212Pb, 224Ra and 223Ra.

ABEX UPTX: 20030616

WIDER DISCLOSURE - The following are also disclosed as new:
(1) nucleic acid molecules encoding (I); and
(2) modifications of PSMA protein multimer.

SPECIFIC ANTIBODIES - Specifically claimed is (I) or its fragment that is chosen from PSMA 3.7, PSMA 3.8, PSMA 3.9, PSMA 3.11, PSMA 5.4, PSMA 7.1, PSMA 7.3, PSMA 10.3, PSMA 1.8.3, PSMA A3.1.3, PSMA A3.3.1, Abgenix

4.248.2, Abgenix 4.360.3, Abgenix 4.7.1, Abgenix 4.4.1, Abgenix 4.177.3, Abgenix 4.16.1, Abgenix 4.22.3, Abgenix 4.28.3, Abgenix 4.40.2, Abgenix 4.48.3, Abgenix 4.49.1, Abgenix 4.209.3, Abgenix 4.219.3, Abgenix 4.288.1, Abgenix 4.333.1, Abgenix 4.54.1, Abgenix 4.153.1, Abgenix 4.232.3, Abgenix 4.292.3, Abgenix 4.304.1, Abgenix 4.78.1, Abgenix 4.152.1 and its antigen-binding fragments (claimed).

ADMINISTRATION - (I) is administered by oral, intravenous, intraperitoneal, intramuscular, intracavity, intratumor, or transdermal route, preferably by intravenous route and pulmonary aerosol. Dosages range from 10-100,000 microg/kg.
EXAMPLE - A panel of monoclonal antibodies (mAbs) to conformational epitopes on prostate-specific membrane antigen (PSMA) was generated as follows BALB/c mice were immunized subcutaneously with recombinant PSMA at approximately three-week intervals, After a total of 4 injections, mice were sacrificed and their splenocytes fused with a myeloma cell line using standard techniques in order to create hybridomas. Individual hybridoma supernatants were screened by enzyme linked immunosorbent assay (ELISA) for reactivity with PSMA derived from either LNCaP human prostate tumor cells or from 3T3 cells engineered to express full-length human PSMA (3T3-PSMA cells). Positive clones were secondarily screened by flow cytometry for specific reactivity with intact 3T3-PSMA and LNCaP cells so as to select antibodies that recognize native cell-surface PSMA and thus have the greatest therapeutic potential. Mice having the ability to produce human antibodies were immunized subcutaneously once or twice weekly with 5x106 LNCaP cells adjuvanted with alum or Titermax Gold. Animals were boosted twice with 10 microg of recombinant PSMA protein immunoaffinity captured onto protein G magnetic microbeads. PSMA mAb 3.11 was used for capture. Splenocytes were fused with NSO myeloma cells and the hybridomas that resulted were screened by flow cytometry to detect clones producing antibodies reactive with extracellular portion of PSMA. One clone, 10.3 (PTA-3347), produced such antibodies. These methods yielded a high proportion of mAbs that react exclusively with conformation-specific epitopes on cell-surface PSMA. Several (mAbs 3.7, 3.9, 33.11, 5.4, and 10.3) but not all (mAb 3.12) mAbs specifically bind viable PSMA-expressing cells. Using recombinant soluble PSMA proteins expressed in Chinese hamster ovary (CHO) cell, lines it further was demonstrated that the mAbs bind epitopes in the extracellular region of PSMA. The mAbs were also tested for their ability to immunoprecipitate native PSMA from 3T3-PSMA cell lysates. The mAbs positive in flow cytometry were also effective in immunoprecipitation whereas mAb 3.12 was unreactive.

L40 ANSWER 6 OF 9 WPIX COPYRIGHT 2003 THOMSON DERWENT on STN
AN 2003-354629 [33] WPIX
DNC C2003-093529
TI New crystalline tetrapeptide useful as an antitumor agent.
DC B03 B04
IN KANADA, A; KEINO, K; MINAMI, N; MIYAZAKI, K
PA (TEIK) TEIKOKU HORMONE MFG CO LTD
CYC 25
PI WO 2003026645 A1 20030403 (200333)* JA 20p A61K031-40
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR
W: AU CA CN JP KR US
ADT WO 2003026645 A1 WO 2002-JP9628 20020919
PRAI JP 2001-286674 20010920
IC ICM A61K031-40
ICS A61K009-08; A61P035-00; C07D207-09
AB WO2003026645 A UPAB: 20030526
NOVELTY - Crystalline N2-(N,N-dimethyl-L-valyl)-N-((1S,2R)-2-methoxy-4-((2S)-2-((1R,2R)-1-methoxy-2-methyl-3-oxo-3-((2-phenylethyl)amino)propyl)-1-pyrrolidinyl)-1-((S)-1-methylpropyl)-4-oxobutyl)-N-methyl-L-valinamide (I) is new.

DETAILED DESCRIPTION - Crystalline N2-(N,N-dimethyl-L-valyl)-N-((1S,2R)-2-methoxy-4-((2S)-2-((1R,2R)-1-methoxy-2-methyl-3-oxo-3-((2-phenylethyl)amino)propyl)-1-pyrrolidinyl)-1-((S)-1-methylpropyl)-4-oxobutyl)-N-methyl-L-valinamide (i.e. **TZT-1027**) of formula (I) or its salt is new.

ACTIVITY - Cytostatic.

No activity data is given.

MECHANISM OF ACTION - None given.

USE - As a crystalline form of the antitumor agent **TZT-1027** useful for preparing oral or injection solutions.

ADVANTAGE - Has improved solubility compared to non-crystalline form.

Dwg.0/2

FS CPI

FA AB; GI; DCN

MC CPI: B07-D03; B12-M11H; B14-H01B

TECH UPTX: 20030526

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: Crystalline (I) is prepared e.g. by dissolving non-crystalline (I) or its salt in diethyl ether or ethyl acetate single solvent or a mixture of an ester or a hydrocarbon and/or an ether (preferably ethyl acetate, n-hexane or n-pentane and diethylether) and crystallizing, then optionally recrystallizing.

ABEX UPTX: 20030526

SPECIFIC COMPOUNDS - One crystalline form is specifically claimed i.e. (I) having the following peaks (d) by X-ray diffraction chromatography: 14.72, 12.27, 9.84, 9.28, 8.68, 7.39, 6.11, 5.32, 5.10, 4.90, 4.61, 4.47, and 4.36 Angstrom.

EXAMPLE - Non-crystalline **TZT-1027** (5.0 g) was dissolved in diethyl ether (20 ml) and stirred at room temperature for 3 hours. The crystalline product was removed and ethyl acetate (25 ml) was added and the mixture was heated to 40-60 degrees C. Diethyl acetate (15 ml) was removed at 110 degrees C and water was added at 30 degrees C with stirring. The mixture was cooled to 10 degrees C an the product was removed, washed and dried to give 4.8 g (HPLC = 99.3 %) of crystalline (I).

L40 ANSWER 7 OF 9 WPIX COPYRIGHT 2003 THOMSON DERWENT on STN

AN 2002-013667 [02] WPIX

DNC C2002-003798

TI Micro-tubule formation promoter for use as anti-tumor agent, is co-administered with PI3-kinase-Akt path blocking agent.

DC B05

PA (TEIK) TEIKOKU HORMONE MFG CO LTD

CYC 1

PI JP 2001247477 A 20010911 (200202)* 6p A61K045-00

ADT JP 2001247477 A JP 2000-58776 20000303

PRAI JP 2000-58776 20000303

IC ICM A61K045-00

ICS A61K031-475; A61K031-5377; A61K038-00; A61K045-06; A61P035-00

ICA C07D311-58

AB JP2001247477 A UPAB: 20020109

NOVELTY - A micro-tubule formation promoter is co-administered with PI (phosphatidylinositol) 3-kinase-Akt path blocking agent.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) an anti-tumor agent containing a combination of micro-tubule formation promoter and PI3-kinase-Akt path blocking agent, as active ingredient; and

(2) a product containing micro-tubule formation promoter and PI3-kinase-Akt path blocking agent, in a packaging material.

ACTIVITY - Cytostatic.

MECHANISM OF ACTION - Tubulin polymerization inhibitor; protein kinase inhibitor.

USE - As anti-tumor agent.

ADVANTAGE - PI3-kinase-Akt path blocking agent efficiently enhances anti-tumor effect of micro-tubule effect agent, hence the combination has excellent synergistic anti-tumor effect. Anti-tumor enhancing effect of 2-(4-morpholinyl-8-phenyl-4H-1-benzo pyran-4-on) (as PI3-kinase-Akt path blocking agent (LY294002)) on vincrystine (as micro-tubule effect agent) was evaluated on T24 cell (a human bladder cancer derived cell) (1.5 multiply 10 to the power 5 cells/9 ml). A combination of 3 nM vincrystine and 4 micro M LY294002 showed cell death rate of 35.28%, 61.64% and 87.93%, whereas individual administration of 3 nM vincrystine in 0.1% dimethyl sulfoxide showed cell death rate of 11.71%, 16.34% and 27.28%, after 24 hours, 48 hours and 96 hours, respectively.

Dwg.0/0

FS CPI

FA AB; DCN

MC CPI: B06-A03; B06-D18; B06-E05; B14-D06; B14-H01; B14-L06

TECH UPTX: 20020109

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Active Ingredient: The micro-tubule formation promoter is tubulin polymerization inhibitor such as drastatin 10 and its compound, or vincristine and its compound (much more tubulin polymerization inhibitor such as maytansine, rhizoxin, paclitaxel, etc., are disclosed). The PI3-kinase-Akt path blocking agent is Akt inhibitor, PI3,4,5-P3 dependent protein kinase (PDK) inhibitor, or PI3-kinase inhibitor.

ABEX UPTX: 20020109

ADMINISTRATION - Micro-tubule formation promoter is administered at a dose of 0.1-1000 mg, preferably 0.5-500 mg once daily and PI3-kinase-Akt path blocking agent at a dose of 0.1-1000 mg, preferably 50-500 mg once daily, both in combination.

EXAMPLE - Suitable quantity of sodium chloride and lactic acid were dissolved in water for injection to form a solution. **TZT-1027** (Drastatin 10) (a micro-tubule formation promoter) (0.2) was dissolved in the solution, pH was adjusted to 4-5 using sodium hydroxide, and quantity was made up to 1 ml with water-for-injection and injection solution was obtained. Tablet containing (in mg/tablet) 2-(4-morpholinyl-8-phenyl-4H-1-benzo pyran-4-on (a PI3-kinase-Akt path blocking agent) (20), starch (5), lactose (132), carboxy methyl cellulose (10), talc (1) and magnesium stearate (2) was prepared.

L40 ANSWER 8 OF 9 WPIX COPYRIGHT 2003 THOMSON DERWENT on STN

AN 2000-545833 [50] WPIX

DNC C2000-162772

TI Antitumor agent comprising Drastatin 10 or a derivative as the active component is used in combination with another antitumor agent containing as the active component(s) e.g. 5-fluorouracil, doxorubicin or cisplatin.

DC B05

PA (TEIK) TEIKOKU HORMONE MFG CO LTD

CYC 1

PI JP 2000191546 A 20000711 (200050)* 6p A61K038-00

ADT JP 2000191546 A JP 1998-373475 19981228

PRAI JP 1998-373475 19981228

IC ICM A61K038-00

ICS A61K031-337; A61K031-505; A61K031-66; A61K031-704; A61K031-7048; A61K033-24; A61P035-00

AB JP2000191546 A UPAB: 20001010

NOVELTY - An antitumor agent comprising (a) Drastatin 10 or a derivative as the active component is used by combining with another antitumor agent containing as the active component (b) one or two compounds selected from 5-fluorouracil, doxorubicin, irinotecan, cisplatin, cyclophosphamide, etoposide and paclitaxel components.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(1) a combination of the above antitumor agents (a) and (b) for treating a tumor by administering an antitumor agent containing (a) and an antitumor agent containing (b) together or separately; and

(2) a drug product containing the above combination and an indication or a document describing the combined use on or in the packaging material.

ACTIVITY - Cytostatic.

USE - For treating cancers.

Dwg.0/0

FS CPI

FA AB; DCN

MC CPI: B02-D; B05-A03B; B05-C01; B05-C07; B06-A03; B06-E05; B07-D03; B07-D12; B14-H01

ABEX UPTX: 20001010

EXAMPLE - 2 mg of **TZT-1027**, 20 mg of cisplatin and 60 mg of a lactic acid-glycolic acid copolymer (50:50, M.W.:ca. 5000) were dissolved in 1 ml of methylene chloride and the solution was dispersed in 150 ml of 0.5 % aqueous polyvinyl alcohol solution and the dispersion was stirred for 2 hours to solidify the oil phase. The microspheres thus formed were collected by centrifugation and washed with pure water and redispersed in water and freeze-dried to give microspheres. For use, they were suspended in a suspension containing 50 mg/ml of mannitol, 5 mg/ml of Na carboxymethylcellulose and 1 mg/ml of Polysorbate 80.

L40 ANSWER 9 OF 9 WPIX COPYRIGHT 2003 THOMSON DERWENT on STN

AN 2000-475770 [41] WPIX

DNC C2000-142630

TI Potentiating antitumor activity of ERK MAP kinase cascade blocking agent using antitumor agent acting on microtubules.

DC B05

IN KOHNO, M; WATANABE, K

PA (TEIK) TEIKOKU HORMONE MFG CO LTD

CYC 24

PI WO 2000040268 A1 20000713 (200041)* JA 23p A61K045-00
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: AU CA JP KR US
AU 2000018049 A 20000724 (200052) A61K045-00
EP 1142583 A1 20011010 (200167) EN A61K045-00
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
KR 2001089740 A 20011008 (200220) A61K031-40
JP 2000592022 X 20020423 (200243) A61K045-00

ADT WO 2000040268 A1 WO 2000-JP2 20000104; AU 2000018049 A AU 2000-18049 20000104; EP 1142583 A1 EP 2000-900040 20000104, WO 2000-JP2 20000104; KR 2001089740 A KR 2001-708338 20010629; JP 2000592022 X JP 2000-592022 20000104, WO 2000-JP2 20000104

FDT AU 2000018049 A Based on WO 2000040268; EP 1142583 A1 Based on WO 2000040268; JP 2000592022 X Based on WO 2000040268

PRAI JP 1999-2971 19990108

IC ICM A61K031-40; A61K045-00
ICS A61K035-00; A61K038-00; A61K038-08; A61P035-00

AB WO 200040268 A UPAB: 20000831

NOVELTY - Use of an antitumor agent (I) acting on microtubules and an ERK MAP kinase cascade blocking agent (II) is claimed. (I) and (II) are administered together or separately at different times.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) an antitumor agent comprising (I) and (II); and

(2) potentiating the activity of (I) by (II).

ACTIVITY - Cytostatic.

In assays using WiDr cells, cell death after 96 hours for a control, **TZT-1027** at 10 nmol/l, PD-98059 at 50 mu mol/l or a combination of **TZT-1027** at 10 nmol/l and PD-98059 at 50 mu mol/l were 3.0, 8.9, 23.3 and 48.1% respectively.

MECHANISM OF ACTION - Microtubule depolymerizer; MAP kinase

inhibitor.
USE - Used as antitumor agents.
ADVANTAGE - Combination is safe and agent acting on microtubules potentiates ERK MAP kinase cascade blocking activity.
Dwg.0/0
FS CPI
FA AB; DCN
MC CPI: B06-D18; B14-D06; B14-H01
TECH UPTX: 20000831
TECHNOLOGY FOCUS - PHARMACEUTICALS - Preferred Agents: (I) is a tubulin binding inhibitor (preferably **TZT-1027** or vincristine or their related compounds). (II) is a MAP kinase inhibitor, a MAP kinase kinase inhibitor or a MAP kinase kinase kinase inhibitor.
ABEX UPTX: 20000831
ADMINISTRATION - The dosage is 0.1-1000 (preferably 0.5-500) mg/day a.i.

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(FILE 'HOME' ENTERED AT 08:16:11 ON 11 DEC 2003)
SET COST OFF

FILE 'REGISTRY' ENTERED AT 08:16:25 ON 11 DEC 2003
E TZT/CN
L1 1 S E6
E C39H67N5O6/MF
L2 7 S E3
L3 3 S L2 AND NC4/ES AND 46.150.18/RID
L4 2 S L3 NOT L1
SEL RN L1
L5 7 S E1/CRN

FILE 'HCAOLD' ENTERED AT 08:20:14 ON 11 DEC 2003
L6 0 S L1

FILE 'HCAPLUS' ENTERED AT 08:20:14 ON 11 DEC 2003
L7 37 S L1
L8 31 S TZT1027 OR TZT 1027 OR SOBLIDOTIN? OR AURISTATIN? PE

FILE 'HCAOLD' ENTERED AT 08:20:21 ON 11 DEC 2003
L9 0 S L1

FILE 'HCAPLUS' ENTERED AT 08:20:22 ON 11 DEC 2003
L10 37 S L1
L11 46 S TZT1027 OR TZT 1027 OR SOBLIDOTIN? OR AURISTATIN? PE OR AURIS
L12 53 S L10,L11
L13 9 S L12 AND (KOHNO ? OR WATANABE ?)/AU
L14 21 S L12 AND TEIKOKU?/PA,CS
L15 1 S L12 AND (WO2000-JP2 OR JP99-2971)/AP,PRN

FILE 'REGISTRY' ENTERED AT 08:47:20 ON 11 DEC 2003
L16 1 S 142243-02-5

FILE 'HCAPLUS' ENTERED AT 08:48:03 ON 11 DEC 2003
L17 7980 S L16
L18 367 S ERK(A)MAP()KINASE
L19 12817 S MITOGEN ACTIVATED PROTEIN KINASE
L20 699 S EXTRACELLULAR SIGNAL REGULATED PROTEIN KINASE
L21 12557 S MAP KINASE
L22 4309 S EXTRACELLULAR SIGNAL REGULATED KINASE
L23 2526 S ERK KINASE
L24 1 S L12 AND L17-L23
E ANTITUMOR/CT

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                E E5+ALL
L25       165939 S E1,E2
L26        20279 S E25,E26
                E E25+ALL
L27         1545 S E3
L28           40 S L12 AND L25-L27
L29           53 S L12,L13-L15,L24,L28
L30           20 S L29 AND (PD<=19990108 OR PRD<=19990108 OR AD<=19990108)

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     FILE 'HCAPLUS' ENTERED AT 08:53:14 ON 11 DEC 2003

     FILE 'USPATFULL, USPAT2' ENTERED AT 08:53:28 ON 11 DEC 2003
L31            4 S L1
L32           37 S L11
L33           40 S L31,L32
L34            4 S L33 AND (PD<=19990108 OR PRD<=19990108)

     FILE 'USPATFULL, USPAT2' ENTERED AT 08:54:25 ON 11 DEC 2003

     FILE 'EMBASE' ENTERED AT 08:55:04 ON 11 DEC 2003
L35           44 S L1 OR L11
L36           13 S L35 AND PY<=1999

     FILE 'EMBASE' ENTERED AT 08:55:53 ON 11 DEC 2003

     FILE 'MEDLINE' ENTERED AT 08:56:14 ON 11 DEC 2003
L37           34 S L1 OR L11
L38           13 S L37 AND PY<=1999

     FILE 'EMBASE, MEDLINE' ENTERED AT 08:56:41 ON 11 DEC 2003
L39           15 DUP REM L36 L38 (11 DUPLICATES REMOVED)

     FILE 'WPIX' ENTERED AT 08:57:02 ON 11 DEC 2003
L40            9 S L11/BIX

     FILE 'WPIX' ENTERED AT 08:57:45 ON 11 DEC 2003

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